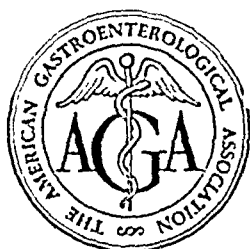




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MARCH, 1949

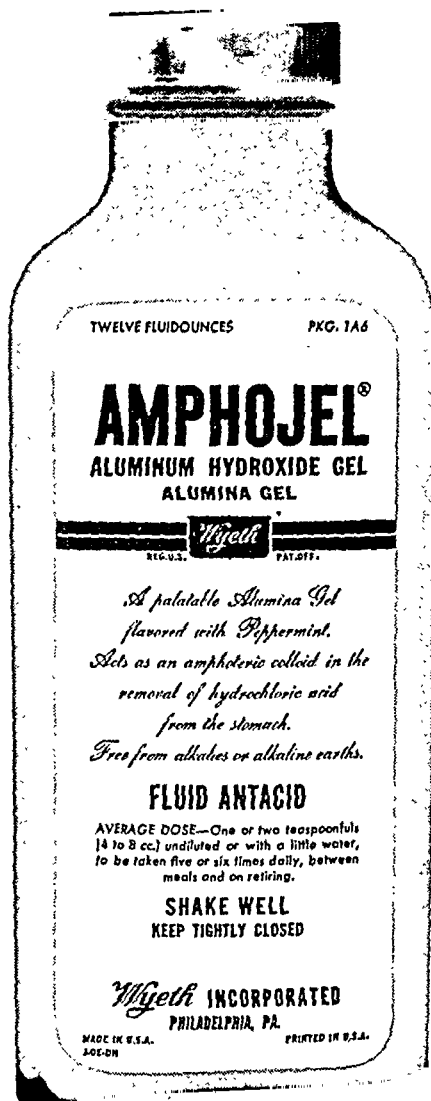
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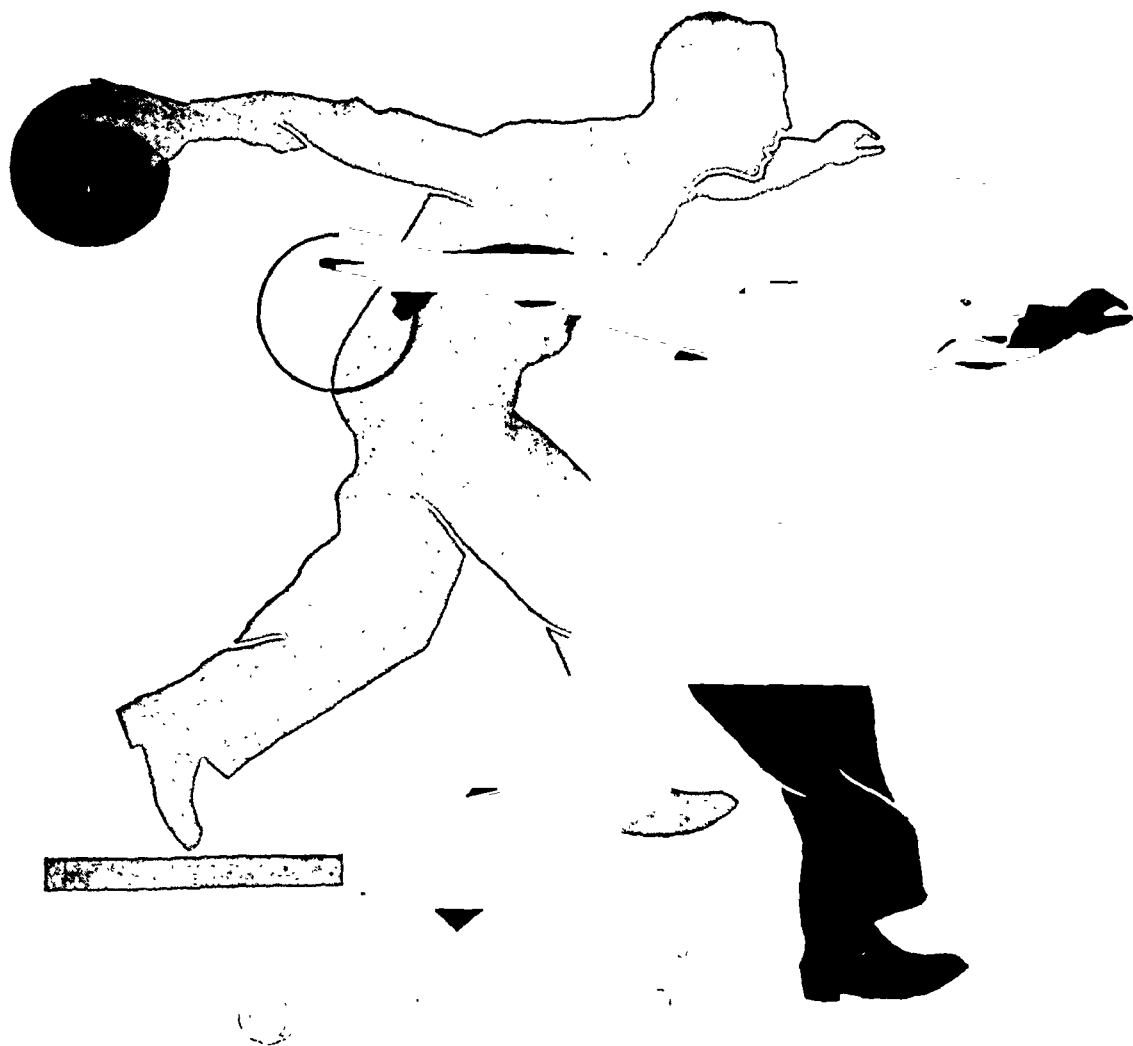
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## VOLUME 12, NUMBER 3

## GASTROENTEROLOGY

*Official Journal of the American Gastroenterological Association*WALTER C. ALVAREZ, *Editor*A. C. IVY, *Assistant Editor*

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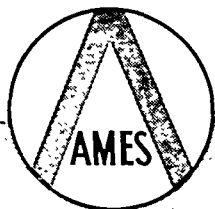
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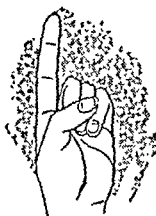
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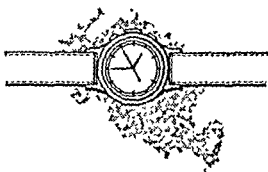
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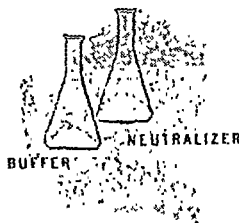
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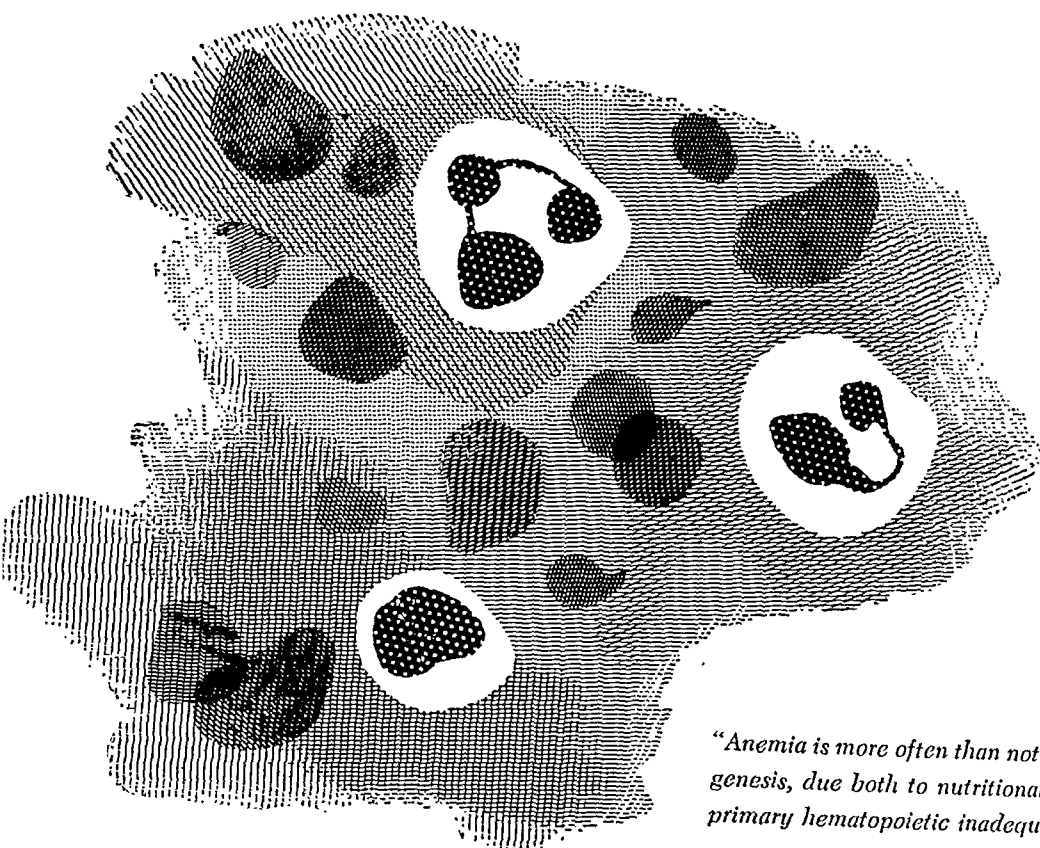
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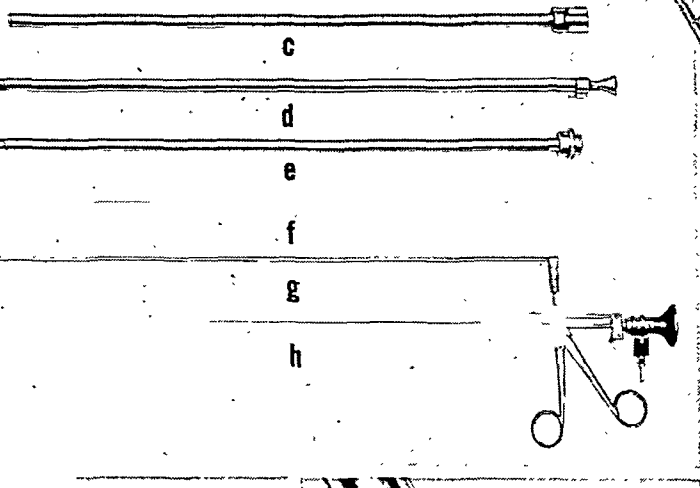
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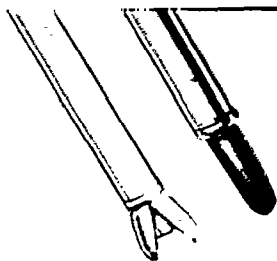


- a. Outer gastroscope sheath with obturator in place for safe insertion.
- b. Obturator replaced by esophagoscopic telescope and inner esophagoscope tube with expanding metal shells.
- c. Outer esophagoscope sheath.
- d. Obturator for insertion in outer sheath.
- e. Inner esophagoscope tube with movable shells.
- f. Esophagoscope telescope.
- g. Light carrier.
- h. Biopsy forceps with operating telescope.
- j. Expanding metal shells which remove mucosa from objective for maximum clarity of field.
- k. Soft rubber, obturator tip, facilitating introduction.



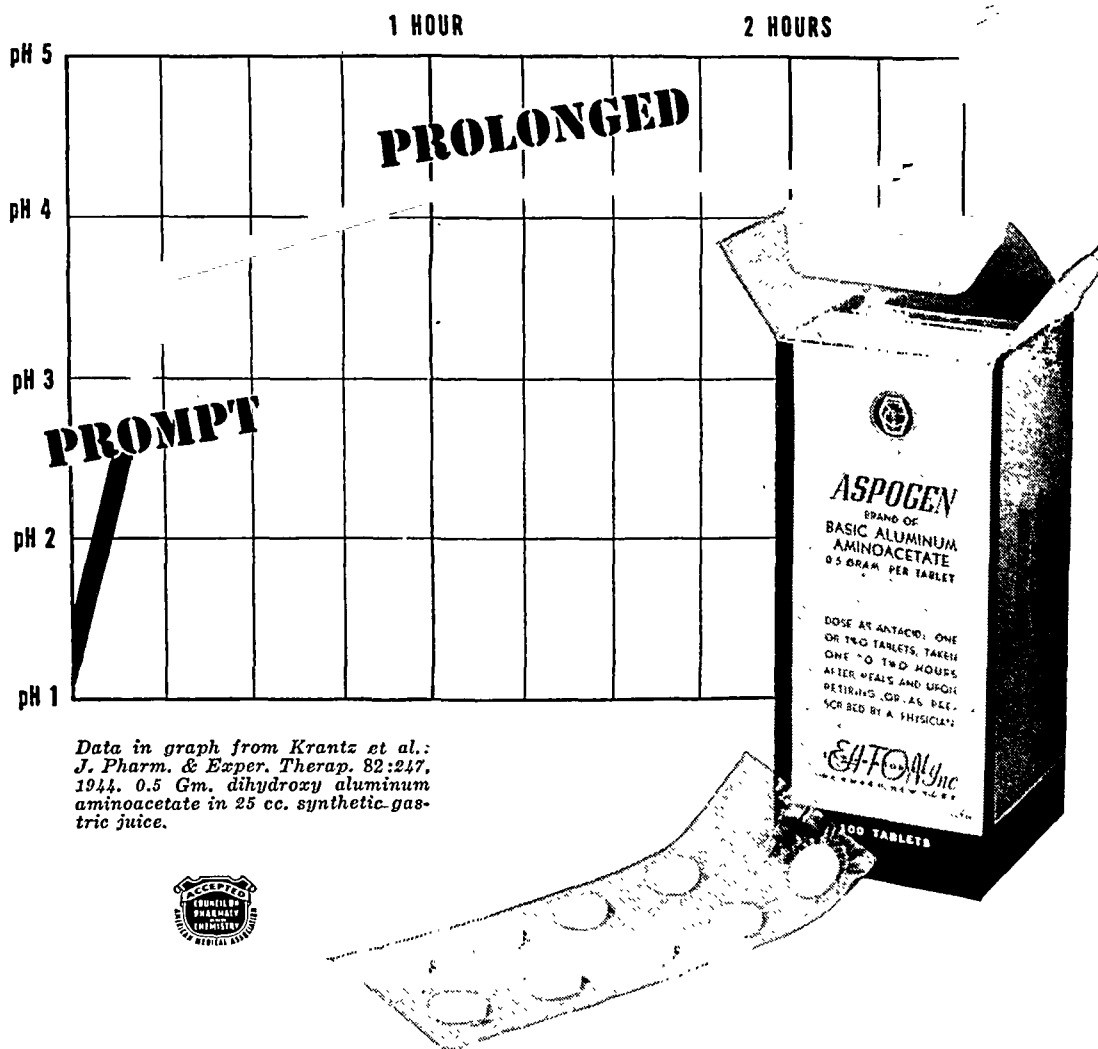
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\*Krantz, J. et al.: *J. Pharmacol. & Exper. Therap.* 82:247, 1944 • Paul, W. et al.: *J. Iowa M. Soc.* 35:167, 1945 • Weissberg, J. et al.: *Am. J. Digest. Dis.* 15:332, 1948.

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1. Grollman, A.: *Essentials of Endocrinology* (Lippincott—Phila., 1944).
2. Carter, Cohen and Shorr: *Vitamins and Hormones* (Academic Press), Volume V, 1947.

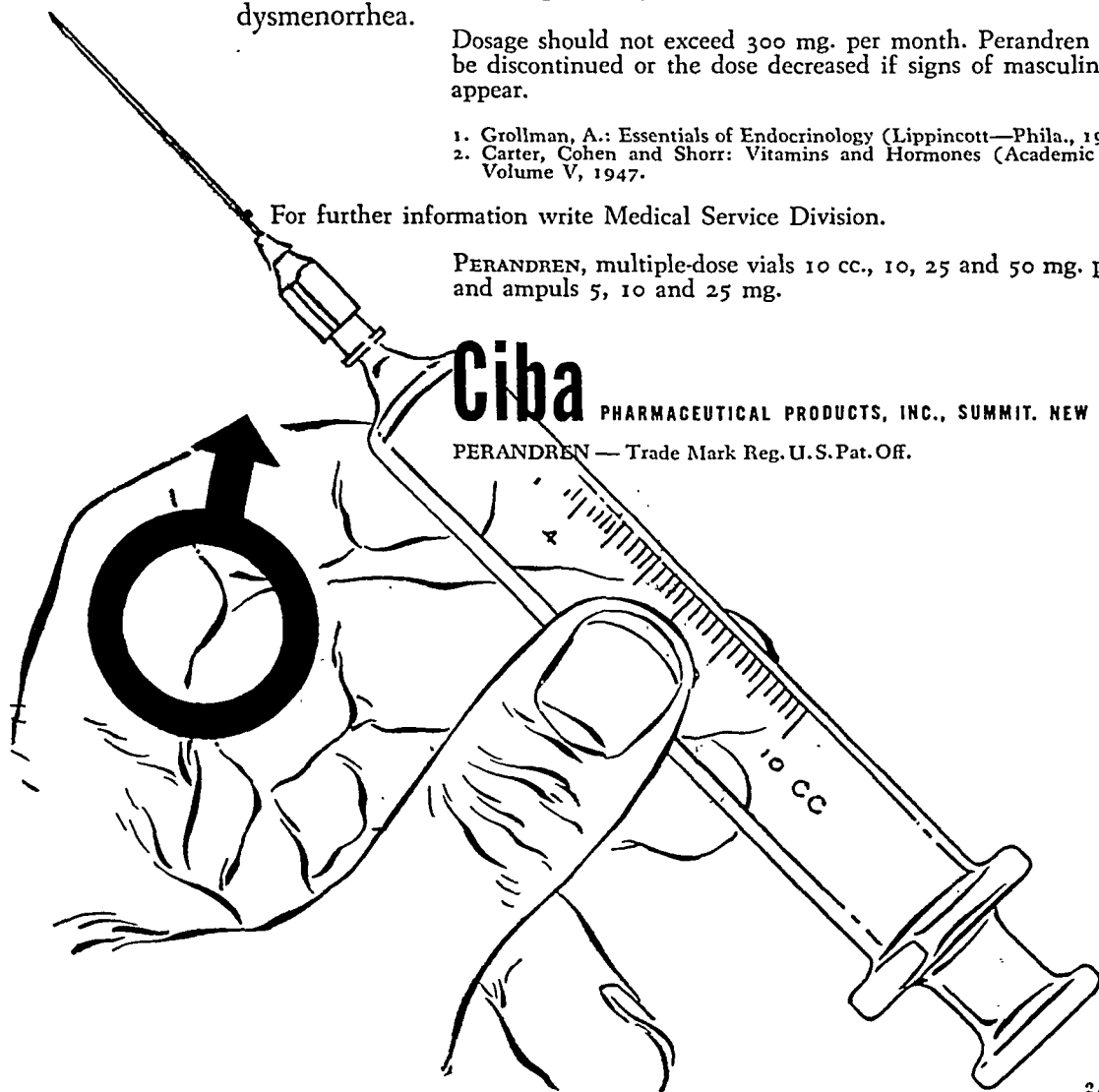
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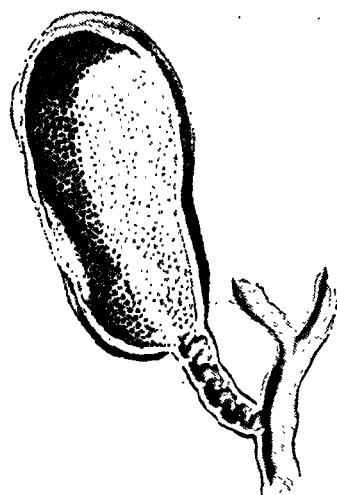
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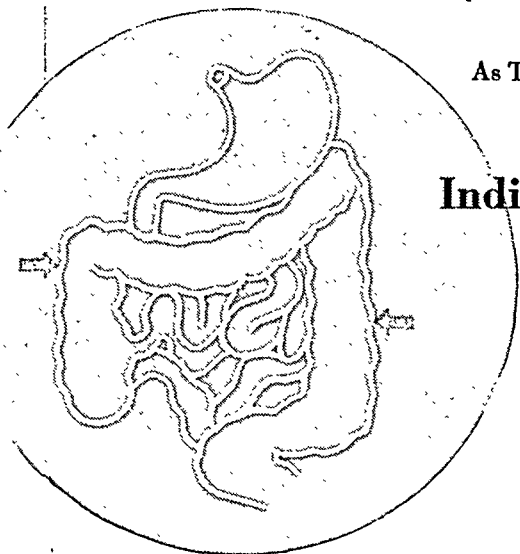
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**bibliography:** 1. Seneca, H., and Henderson, E.: In press. 2. Heineken, T., and Seneca, H.: Rev. Gastroenterol. 15:611, 1948.

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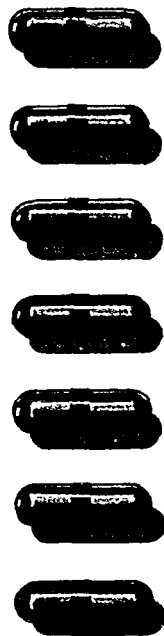
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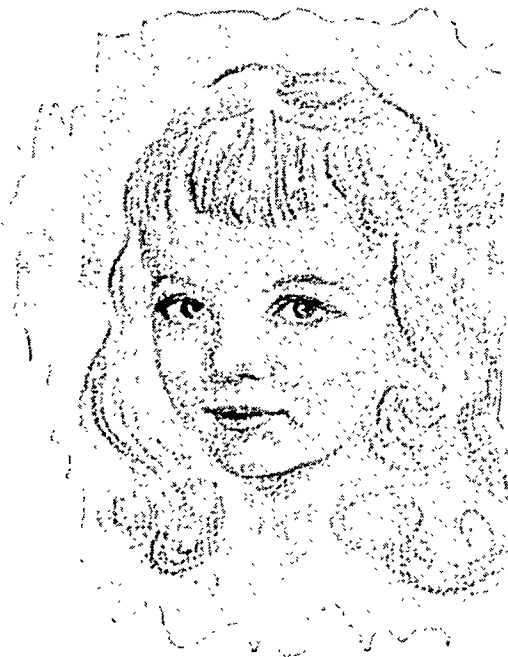
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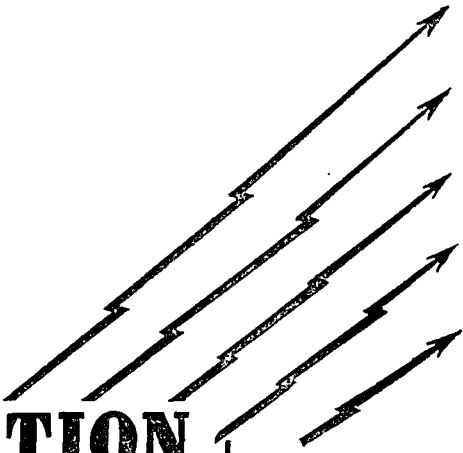
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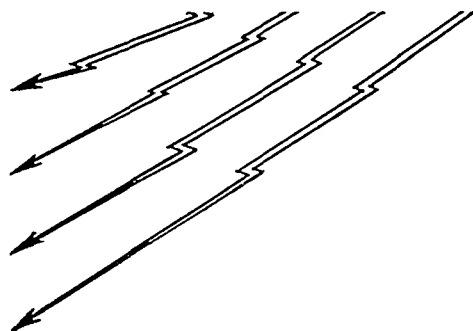
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*1. Weiss, J.: Review of Gastroent., 15:826, Nov., 1948.*

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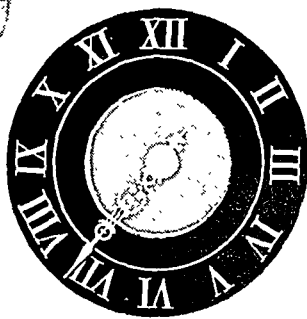


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## CONSTRUCTION AND USE OF A SAFE DIAGNOSTIC OPTICAL ESOPHAGOSCOPE

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For a long time it has been the wish of internists and surgeons to have at their disposal an esophagoscope permitting safe, easy and clear inspection of the esophagus. Esophagoscopy at present is difficult and is not safe. An endeavor has been made to construct a safe diagnostic esophagoscope, easy to handle and giving large clear images. The principles of construction have been described elsewhere\*. They will be summarized here briefly. This paper intends to give a description of the new instrument and of its use.

### PRINCIPLES

Open tube esophagoscopy not infrequently leads to hypopharyngeal tears with ensuing mediastinitis and—sometimes—death. This lesion almost never occurred at the introduction of rigid gastroscopes, which contained a flexible rubber obturator. The reason for this difference is found in the anatomy of the hypopharynx. One would not try to introduce an open proctoscope through the constrictor muscle of the anus. A similar constrictor muscle is found at the entrance of the esophagus, the inferior constrictor muscle of the pharynx. This, in contrast to the anal sphincter muscle, is sometimes open, especially if a swallowing movement is made. Then an open instrument can be introduced under the control of the eye. Such opening may be of short duration, however, and sometimes the pharyngeal constrictor muscle remains tightly closed. In this case an open instrument cannot be introduced for the same reasons that an open tube cannot be introduced through the anal sphincter. All leading esophagoscopists have warned against introducing an esophagoscope if the lumen of the esophagus is not plainly visible.

A tube equipped with a flexible rubber obturator is not apt to produce a lesion, if its diameter is not too large, as long experience with the rigid gastroscope has proved. If the constrictor muscle is open the obturator, if guided properly, enters the esophagus without difficulty. If the constrictor muscle is closed, but not spastically, a rubber obturator will disengage its walls, as the

\* Journal American Medical Association, 138:885, 1944.

obturator of the proctoscope disengages the walls of the anal canal. If the muscle is spastically closed, no instrument can enter; the rubber obturator then will bend, but it will not produce a lesion.

This reasoning is true only if the diameter of the esophagoscope is not too large. The antero-posterior diameter of the entrance of the esophagus is supposed to be about 15 millimeters, or with some extension 17 millimeters. Instruments with a diameter of 15 millimeters are not safe. They easily produce a tear, even if introduced with an obturator. It is difficult to determine what the maximum diameter for safe introduction is. It probably lies between 11 and 12 millimeters. The Schindler rigid gastroscope of 1922 had a diameter of 11 millimeters and hypo-pharyngeal lesions were not caused by its use. If the diameter of an esophagoscope is reduced so much the image observed becomes very small. Clear visualization and interpretation is not easy even with larger instruments and may be still more disturbed by secretion or bleeding. The internist, accustomed to the large brilliant pictures of cystoscopy and gastroscopy, often experiences diagnostic difficulties if confronted with the small esophagoscopic pictures. If a diameter of 11 millimeters or less is chosen the picture becomes too small. Yet, such a diameter is desirable not only from the viewpoint of safety but also for the comfort of the patient. Therefore, construction of a magnifying optical apparatus seemed desirable. The question was whether to construct an outer telescope or an inner optical system, such as used in cystoscopes and gastroscopes. This latter system certainly yields beautiful magnification and brilliant pictures. The fear that it may become too easily soiled was dispelled by preliminary attempts made with a make-shift instrument in 1943. The war delayed the final construction. In the following paragraphs the diagnostic esophagoscope will be described as it is now built by the American Cystoscope Makers. Attempts to add therapeutic attachments—as foreign body forceps and injection needle—will be made. Here only the diagnostic instrument will be described.

#### THE INSTRUMENT

The esophagoscope consists of (1) the outer tube with obturator, (2) the inner tube with two spreading "shells" at its tip, and (3) the optical tube which carries the source of light, the optical system and two air canals. This optical tube can be exchanged for (4) the biopsy forceps which also is attached to an optical system.

##### *(1) Outer Tube and Obturator (Figs. 1 and 2)*

The outer tube has a diameter of only 10 millimeters. Thereby the discomfort of the patient is reduced to a minimum and the safety increased to a maximum. This diameter permits the use of the instrument in children.

The length of the usable portion of the instrument was originally 40 centimeters,—the average distance between the teeth and the cardia, and this length is still shown in the pictures. It was thought that the inspection of the stomach would be better accomplished by the gastroscope. Yet, a case was encountered in which a tumor of the fornix prevented introduction of the gastroscope, but could not be reached with the 40 centimeter esophagoscope. Therefore, the instrument now has a length of 46 centimeters. Its outer surface has marks engraved in distances of 1 centimeter which permit the assistant to



FIG. 1. Outer tube with obturator.



FIG. 2. Tip of outer tube with obturator.

announce to the operator, how far away from the teeth the tip of the optical system is. At the oval end of the usable portion of the tube there is an enlargement which prevents further introduction. It contains a cutout the significance of which will be explained later. It also contains a hole for the pin of the inner tube. This hole can be used for the introduction of a separate light carrier (not pictured) which permits observation through the open tube. It may be used especially for the mechanical cleaning of the visual field by swabs.

From experiences with the rigid gastroscope it was known that an obturator provides absolute safety only if it closes the gastric end of the tube hermetically. Even a slight gap produces a cutting edge at the end of the tube and pinching or tearing lesions become possible. A simple rubber obturator is not

sufficient. Therefore, the construction was chosen which is shown in Figure 2. The obturator is a rubber finger attached to a metal rod. The metal rod fits tightly into the esophagoscopic tube and projects from it a few millimeters. Free edges are thereby avoided. In the majority of cases a rubber finger 6 centimeters long may be employed. It facilitates the introduction of the instrument. For the examination of lesions of the upper portions of the esophagus a 4 centimeter rubber finger is more suitable. Experts may even occasionally use a 2 centimeter rubber finger.

At its upper, oral, end the obturator is provided with a suitable handle.

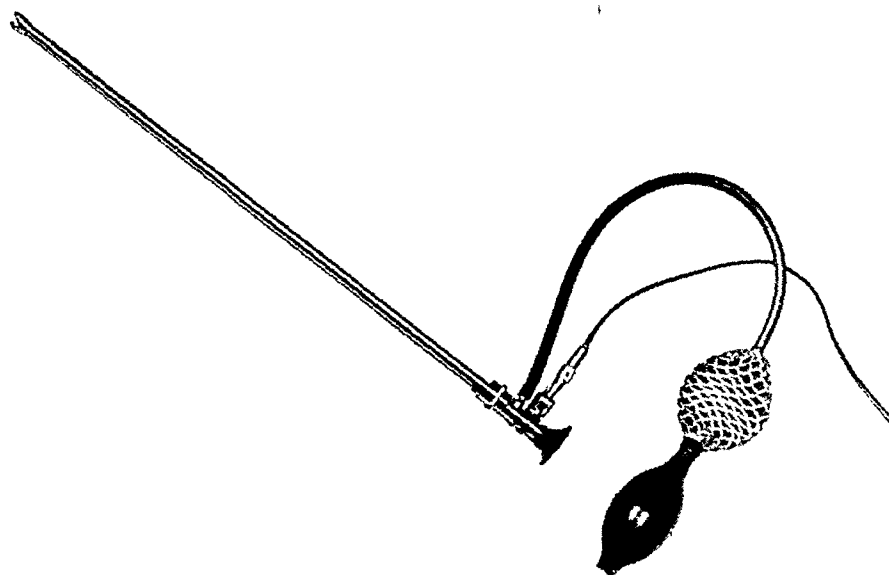


FIG. 3. Inner tube. The "shells" at the tip are spread by the wheel visible just above the attachment of the air balloon.

## (2) *The Inner Tube (Figs. 3, 4, 5 and 6)*

The inner tube fits tightly into the outer tube. At its gastric end two movable metal "shells" are attached (Fig. 4), which can be spread by the action of a wheel at the oral end. This wheel is shown in Figure 3. The purpose of this spreading device is to remove the mucosa from the objective of the optical system so that a picture can be obtained. The spreading mechanism is constructed so that at utmost spreading the greatest outer diameter is 15 millimeters (Fig. 5). The oral end of the inner tube carries a pin which fits into the hole in the outer tube.

After removal of the obturator the inner tube is introduced into the outer tube. This procedure would be rather difficult if the outer tube contained a round hole into which the inner tube had to be fitted. But the cutout of the



FIG. 4. Tip of inner tube. "Shells" closed.

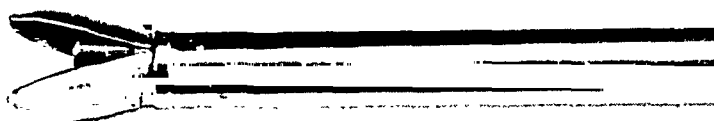


FIG. 5. Tip of inner tube. "Shells" open. The tip of the optical tube is visible.

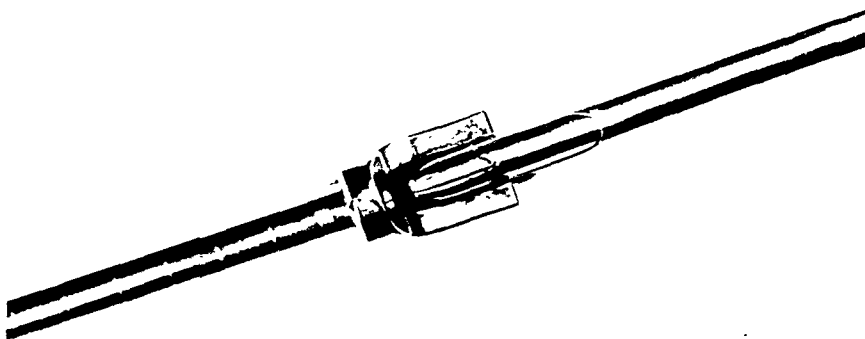


FIG. 6. Introduction of inner tube into outer tube, facilitated by cutout of outer tube.

outer tube (Fig. 6) renders this maneuver simple. The tip of the inner tube with the closed shells is laid from above into the channel formed by the cutout and then readily glides into the outer tube.

(3) *The Optical Tube* (Fig. 7)

The optical tube is usually introduced together with the inner tube. It can be removed, however, for cleaning purposes, for exchanging of the lamp or for replacement by the biopsy forceps. It fits loosely into the inner tube, but can be stabilized within it after full introduction by a short turn to the right. It consists of (a) the optical system, (b) the light carrier, and (c) two air channels.



FIG. 7. Optical tube. The optical system and the light carrier are demonstrated. Between them is the one air channel.

(a) The optical system is an endoscopic system, such as used in cystoscopes, rigid gastroscopes, et cetera—with an important deviation, however. In most optical endoscopic instruments the observer wants to see into a large cavity at the end of a canal: bladder, stomach, pleural and peritoneal cavity. The light coming from the illuminated wall of such a cavity must be deviated into the optical axis of the instrument. For this purpose mirrors or prisms are needed. No such deviation is necessary in the esophagoscope. The observer wants to look into the axis of the instrument itself. Therefore, the optical system of the esophagoscope consists of the objective without prism, of erector systems and of the eyepiece. The objective collects the rays and forms a real image. The erector systems transmit the image through the long tube and cause it to become upright and correct-sided. The eyepiece through which the examiner observes magnifies the small real image which has been formed in

its focal plane and thereby transforms it into a virtual picture. This optical system resembles that of a urethroscope, except for its length.

(b) The light carrier consists of a long metal tube carrying a small electric lamp. A sliding contact distal to the eyepiece connects the instrument with a detachable cable. The cable can be attached to any simple electric battery.

(c) Two air channels—simple hollow tubes are attached at the sides of the light carrier. They are both in connection with an attachment for an air balloon or for a suction apparatus. It may be mentioned here that suction has not proved to be favorable for cleaning the visual field. Usually the picture is clear. Disturbing secretion is best removed or dislocated by blowing air through the air channels into the esophagus.

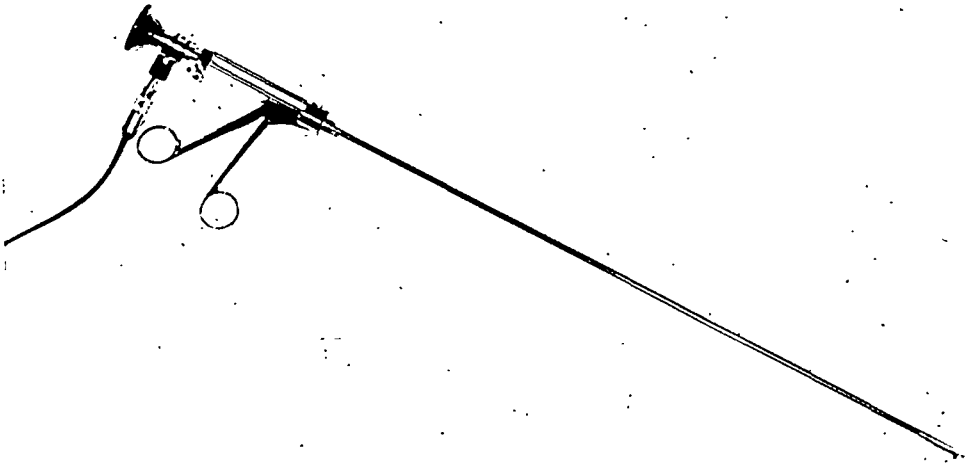


FIG. 8. Biopsy forceps.

When the optical system is fully introduced, objective and lamp lie inside the shells as shown in Figure 5.

#### (4) *The Biopsy Forceps (Figs. 8, 9, 10, 11)*

The biopsy forceps consists of an optical tube (with objective, erector systems and eyepiece), joined solidly to a light carrier and to the outer of the two cup bearing jaws of the cutting forceps. The inner jaw is attached to a tube which slides upward on the optical tube, when the handle of the instrument is closed. The biopsy forceps lies loosely within the inner tube too. It can be advanced into the lumen of the esophagus through the opened shells by about 2 centimeters. Taking of biopsies with this device has not been difficult. Figure 8 shows the entire biopsy forceps, Figure 9 its tip with closed jaws,



Figure 10 the tip with open jaws. Figure 11 demonstrates the relationship of the cups of the biopsy device to lamp and optical objective.

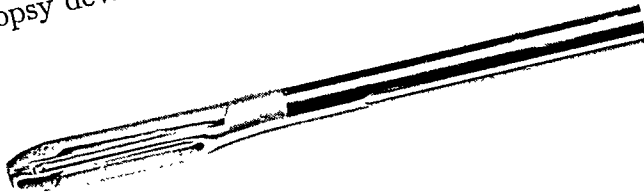


FIG. 9. Tip of biopsy forceps. Jaws closed.



FIG. 10. Tip of biopsy forceps. Jaws opened.

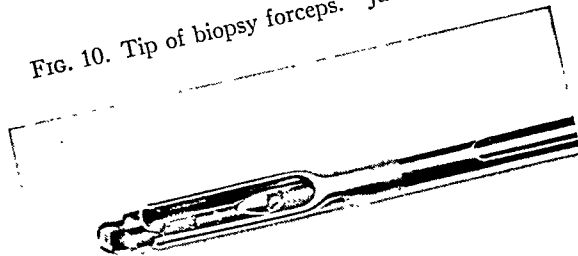


FIG. 11. Tip of biopsy forceps. View permitting one to see the relationships of optical system, light carrier and jaws.

#### TECHNIC

Very brief instructions for the use of this instrument will be given. They refer only to diagnostic esophagoscopy. The recommendations about the position of the patient appear to be important and probably new.

#### 1. Exclusion of Contraindications

Diagnostic esophagoscopy should be preceded by x-ray examination of the esophagus. Several days should elapse between x-ray examination and esophagoscopy. The following conditions, if found at x-ray examination, con-

stitute contraindications for esophagoscopy with the new diagnostic esophagoscope: Obstruction immediately below the constrictor muscle of the pharynx; pulsion diverticulum; aortic aneurism if it compresses the esophagus; and acute corrosive esophagitis.

## 2. *Preparation of the Patient*

Dysphagia will be the most frequent indication. If chronic obstruction is suspected or proved by preceding x-ray examination, the patient should have fluid food only for at least twenty-four hours. One-half hour before the examination he receives a subcutaneous injection of 1/100 grain of atropine sulfate and 2 grains of sodium phenobarbital. The atropine will reduce salivation and esophageal secretion, the barbiturate will counteract toxic effects of the local anesthetic. The local anesthesia of the hypopharynx should be perfect. It should be done as recommended for the use of the flexible gastroscope. 2 per cent pontocain solution with addition of a few drops of adrenalin solution (1:1000) should be used. Pontocain, sometimes dangerous on the cylindrical epithelium of the bronchi, is safe on the squamous epithelium of the pharynx. The total amount should not be more than 4-5 cubic centimeters. If open wounds are present, especially after extraction of teeth, it should be used with the greatest caution or not at all. Pentothal sodium for intravenous injection should always be ready.

If obstruction is suspected the esophagus should be emptied by gravity ("position of the hanging head" or Trendelenburg position). A soft Ewald tube *with closed lower end* and side holes should be used. It should not be introduced to the level of the suspected obstruction in order to prevent artificial hemorrhage. If it is slowly withdrawn, fluids and secretion will empty satisfactorily. Washing of the esophagus with subsequent draining may become necessary in some cases.

## 3. *Position of Patient*

In the past all kinds of positions have been used in esophagoscopy: sitting position, left or right side lying position, supine position, knee-elbow position, et cetera. For the visual introduction only the supine position can be considered and is used exclusively at present. The return to the obturator method necessitated a reconsideration of the most suitable position. Early esophagoscopists, especially Brünings, had recommended the left side position. This is the standard position for gastroscopy. The patient likes this position because the disturbing saliva will flow freely from the left angle of the mouth if the assistant pulls it back gently from time to time. From experience with the rigid gastroscope it was known how easily a rigid instrument with obturator can be introduced in this position. Therefore the left lateral position was

chosen. The head must naturally project beyond the edge of the examination table, so that it may be freely moved by the assistant.

All this corresponds exactly with the usual gastrosopic procedure. However, the question of esophageal secretion had to be considered. Former esophagoscopists (Starck) recommended the Trendelenburg position (head lower than stomach), so that the esophageal contents in cases of obstruction and dilatation would drain through the esophagoscopic tube. If the esophagus is emptied before the examination through an Ewald tube or even lavaged, it will be found clean and empty, and Trendelenburg position is unnecessary. Yet, secretion forming during the examination may still tend to obscure the visual field and especially to smear the objective of the optical system and the electriclamp. The usual suction was tried, but was not found very satisfactory.

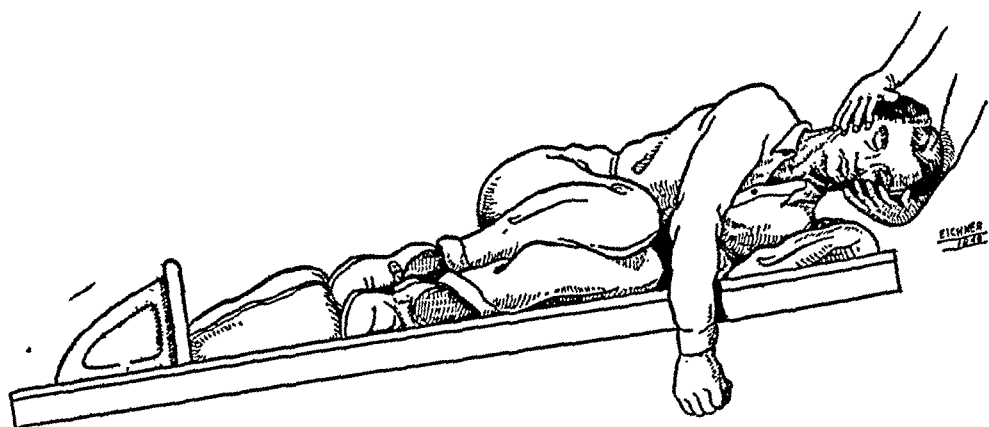


FIG. 12. Left lateral position with reverse Trendelenburg position, as recommended for the use of the optical esophagoscope. Note angle of table, placing mouth above level of stomach. Knees are drawn up as high as possible.

The esophageal mucosa was easily sucked into the tube, and secretion also entered the tube thereby obscuring the image. These difficulties were eliminated at once when *reverse Trendelenburg position* was tried. It seems that this position—patient lying in the left lateral position, but with the head and mouth considerably higher than the stomach (Fig. 12)—has never before been suggested for esophagoscopy. Yet, when using this position there is no longer any disturbance by secretion. Increased secretion, instead of flowing into the tube, will tend to flow toward the stomach. Even in cases of cardiospasm it will sometimes pass the spasm and enter the stomach or it may form a little pool on the left side of the distended lower esophagus where it does not disturb the examination. In this position a clear brilliant picture is almost always obtained. If there should be blurring in the beginning, some air blown through the air channels will produce a clear picture. In ulcerated tumors bloody secretion may cause some transitory difficulties. It then is best to

remove the optical system and to clean lens and lamp with lens paper. Sometimes mechanical cleaning with cotton swabs may be necessary. If it is deemed too dangerous to introduce them blindly, the inner tube may be removed, the light carrier may be inserted and the cleaning may be effected under visual guidance. From present experiences it can be said that such situations are rare and easily remedied in the described position.

For diagnostic esophagoscopy, therefore, the left lateral position with freely movable head in combination with reverse Trendelenburg position is recommended. It cannot be stated whether or not this position would be useful in therapeutic esophagoscopy, especially for the extraction of foreign bodies.

#### THE ESOPHAGOSCOPIC EXAMINATION

The following description is very short and intends only to describe the use of the new instrument, but not to give complete instructions in the art of esophagoscopy.

There is no need to darken the room. The light should not be too bright, however.

If the patient is in the correct position he drops his head heavily into the left hand of the first assistant. Only when the neck muscles are completely relaxed should the introduction begin.

The assistant at first keeps the patient's head in the natural upright position, if the 6 centimeter rubber finger is used. If the 4 centimeter or the 2 centimeter finger is used, the head must be in extension from the first. No extreme extension is permissible.

The operator grasps the outer tube from below in its midportion like a pen and introduces the rubber finger over the back of the tongue into the pharynx of the patient. When the rubber finger points downward the right hand leaves the midportion and seizes the oral end of the instrument, the thumb pressing slightly on the handle of the obturator, thereby preventing it from slipping out. In the meantime the gastric end of the instrument is gently supported by the left thumb. The left index finger may be introduced into the patient's mouth and keep the rubber finger in the mid-line and on the posterior wall of the pharynx. If the instrument is advanced quietly the rubber finger will often enter the hypopharynx without any difficulty. The patient may be asked to make a swallowing movement. As he swallows the pharyngeal constrictor muscle will open and with proper timing the rubber finger can be easily introduced into the hypopharynx. In rare cases the muscle remains spastically closed. One should naturally never try to overcome the spasm by crude force. Quiet waiting will usually lead to the necessary relaxation.

As soon as the rubber finger has entered the hypopharynx the assistant extends the head of the patient (if the 6 centimeter rubber finger has been used).

The thin metal tube then will readily follow the advancing rubber finger and will enter the hypopharynx imperceptibly or with a little jerk. If the tube lies well in the esophagus, the obturator is withdrawn, while the left hand fixes the outer tube. Because of the recommended position the instrument has a certain tendency to slide down the esophagus by gravity. This should be prevented. The inner tube with fastened optical tube and attached cable is then taken with the right hand, its tip is laid into the groove of the cutout of the outer tube and then advanced into the outer tube. For the last 2 centimeters it is better to withdraw the outer tube over the inner tube, if possible, in order to avoid superficial lesions of the mucosa. If this is not possible because of a high lesion the final introduction of the inner tube should be done slowly and without pressure and care should be taken that the pin enters the hole of the outer tube. Then the light is switched on, and the observer, when he looks through the eyepiece, will see the metallic inner surface of the closed shells. The left hand continues to hold the outer tube in place; the right thumb and index fingers grasp the wheel and turn it to the right as far as possible. The opening of the shells is observed. Only their edge can be seen in the visual field.

In this first moment the picture is sometimes slightly blurred. In this case the air balloon is attached and some air is blown through the air channels. The blurring will disappear quickly. The further procedure in the case of disturbing pathologic secretion has been described previously.

If during the examination the entire inner tube must be removed, one should close the shells carefully under constant visualization and under constant rotation, so as to be sure that no mucosa has been grasped.

The advancing of the tube is done with the shells fully opened under guidance of the eye. The shells glide easily down and the patient feels no discomfort. Often the whole circumference of the esophagus can be observed for a depth of about 5 centimeters. Sometimes, especially in dilatations and in the lower segments only portions of its wall appear in the visual field. Adequate inspection of all parts of the wall is secured by proper movements of the patient's head. The assistant should carry them out rather imperceptibly. The posterior wall is visualized by bending the head forward, the anterior wall by taking it backward, the left one by lifting the head, the right one by lowering it. The lumen must be visualized constantly. In the diaphragmatic portion the esophagus turns to the left. There it may become necessary to lift the head considerably and at the same time to press the instrument into the right angle of the mouth. Greater extension of the head may be needed. If no obstruction is present, and even in some cases of cardiospasm, the esophagoscope will usually enter the stomach without difficulty.

Pathologic changes are properly inspected. If a biopsy seems desirable the optical tube is loosened with a short turn to the left and withdrawn. The biopsy forceps is inserted. After obtaining the tissue the biopsy forceps is again replaced by the optical tube. Then the instrument is slowly withdrawn with opened shells and the esophagus is inspected for a second time. As one approaches the pharyngo-esophageal junction, from about 20 centimeters on, it is advisable to close the shells slightly, *but not completely*. The instrument is further withdrawn under guidance of the eye until the back of the tongue appears.

## THE JOYS OF TAKING A HISTORY

### THREE CASE REPORTS

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Following is a close approximation to three actual experiences. Notes were made rapidly as the patient talked. In the first case a rather fluttery-looking woman came into the office and said that her sufferings were so great that unless something were soon done for her, she would have to do away with herself. The physician said, "Well, what seems to be the main trouble?" Her answer was, "I have so many troubles that I don't know where to begin."

"Well, let's begin somewhere."

"All right," said the patient, after thinking a while, "You wouldn't call these little brown, liverish spots on my hands normal, would you?"

"No," said the doctor, but "I wouldn't worry about them. Let's now get down to business. What is your outstanding symptom?"

"I have had it a long time."

"Yes, but what is it?"

"I had my gallbladder out in 1923."

"No, we'll go into that later; what I want to get straight is, what is bothering you most right now?"

"My doctor said he was looking for bleeding."

"No," said the doctor, now deciding that, as a bit of research, he'd like to see how long this sort of thing could be kept up. "No, I asked what your worst symptom was?"

"They put me on a milk and toast diet."

"No, let's get back to the question, 'What would you say bothers you most?'"

"Ulcers, I guess."

"No, that is someone's diagnosis: I want to know what your worst symptom is."

"I still have the same symptoms!"

"Now, perhaps, we are getting somewhere; what are those symptoms?"

"In the last few years I have been eating everything."

"No, again we are straying from the subject, 'What is your main trouble?'"

"Do you think I should be so constipated?"

"We will take that up later: what is your main symptom?"

"My sister says that no one should ever be as constipated as I am."

"No, that is not what I want. I want to know what is bothering you most."

"I went to the store to see a customer. She said, 'Take some herb tea and you'll be better.'"

"No, just for fun, let's stick to the question until we find out what is bothering you most."

"My doctor said the ulcer was active on its outer edge."

"No, that does not help me; what is your main trouble?"

"My doctor gave me a bottle of green medicine. Would you like to see it?"

"No, that wouldn't tell me anything; can't you tell me what is bothering you most?"

"I should say I was just sick!"

Whereupon the physician gave up in despair; he remembered T. A. Ross's statement to the effect that persons who answer questions irrelevantly in this way are mildly insane; their brain is disorganized and not functioning well enough so that they can tell what is wrong with them or can profit from any psychotherapy.

Another woman, a rather nice-looking ex-school teacher of forty-five years, came in one day. She was married to a university professor. When asked what her trouble was, she said, "Asthma." The physician asked, "But what are your symptoms?" She said, "Hadn't you better tell me what I should have?" "No," said the doctor, "I'd prefer to hear from you what the symptoms actually are."

"My doctor gave me a vitamin concentrate."

"No, let's get back to your main symptom."

"I don't know. I'd prefer to have you tell me that I haven't asthma."

"I can't do that until you tell me something of your symptoms."

"They gave me 200 skin tests."

"We'll go into that later; now I'd like to know what your main symptoms are."

"My aunt had a lot of funny symptoms and got operated on."

"I'll ask about her later; do you ever have attacks of wheezing?"

"You know, I don't like my allergist."

About this time the physician decided life was too short and went out in the waiting room to find the husband and see if more could be learned from him. The professor admitted that T. A. Ross was probably right; he had long suspected that his wife was mildly and harmlessly insane. On one occasion he had had her for a time in a psychiatric institute.

Most interesting and baffling was the case of an instructor in psychology at one of the world's greatest universities. When, for ten minutes, he had answered questions in the irrelevant and baffling manner just described, I thought, "What a wonderful opportunity perhaps now to get from a trained observer and student of mental processes some explanation for this curious behavior."

Accordingly, I told him what he had been doing to me and asked him if he



could explain his behavior. After traveling 1,500 miles to see me, surely he must have wanted to co-operate so as to get something out of his trip. He said, "Yes," he surely was miserable and wanted help, but he didn't realize he had done anything unusual, and hence he could not explain his behavior. He was no more helpful to me later when again he thwarted every effort I made to find out what was distressing him. My only conclusion at the end was that his mental processes were badly disorganized. It was hard to understand how, under the circumstances, he could keep on teaching college students. Perhaps he was getting by because he was teaching a subject which at best is a bit unintelligible!

At any rate, one thing the physician in every specialty can be sure of is that this inability to answer questions indicates a disorganized mind. The diagnosis can be made in two minutes. Many a time, when a good assistant has apologized for turning in a vague, unsatisfactory history, I have reassured him instantly by saying that with forty odd years of experience back of me, I would probably fail just as unhappily as he had. It wasn't his fault—it was the patient's.

## PRELIMINARY REPORT OF A CLINICAL TRIAL OF ORALLY ADMINISTERED HOG DUODENUM POWDER IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS

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Chicago*

### INTRODUCTION

In 1945 Gill<sup>1</sup> published the first report on the use of preparations of hog intestine in the treatment of chronic ulcerative colitis. He introduced this form of therapy on the basis of the theory that ulcerative colitis might be a deficiency disease and that the deficient factor might be contained in the intestines. Gill reported on 10 cases treated with either raw pig's small intestine or a desiccated and defatted preparation of pig's small intestinal mucosa. Seven of these 10 cases showed marked symptomatic improvement within one month after beginning treatment with decrease in the number of bowel movements per day, disappearance of blood from the stools and subsidence of pain. Several of the patients who were benefited by the treatment were observed to develop an exacerbation when the administration of the intestinal powder was stopped and to undergo remission again with resumption of the medication. This cycle was repeated several times in two of the patients.

In a subsequent report Gill<sup>2</sup> stated that this therapy was continuing to show beneficial effects. Friedman<sup>3</sup> has recently reported favorable results with the feeding of extracts of hog intestine in patients with ulcerative colitis. Ehrlich<sup>4</sup> fed extract of hog stomach and claimed excellent results.

The present study was prompted by Gill's report.

### HOG DUODENUM POWDER

The preparation used in this study is a simple desiccated defatted powder made from fresh whole hog duodenum by a process which largely prevents protein denaturation (Viodenum, prepared by and kindly supplied by the VioBin Corporation, Monticello, Illinois). The powder was stamped into 0.5 gram tablets. The daily dose was 24 of these tablets in divided amounts during the day. The material is a tan powder with a slight odor and taste but is not offensive and was readily accepted by the patients.

### PATIENTS STUDIED

The subjects of this study were 28 patients with chronic ulcerative colitis whom we had followed for 1 to 1½ years or longer before this study was begun. During this time they had received most of the standard therapies for this

disease including sulfathalidine and oral penicillin. This period of observation before administering duodenal substance provided us with accurate data on the severity and course of the disease in each patient to serve as a base line on which to judge the efficacy of the new treatment.

TABLE 1

*Number of Stools per Day and Number of Exacerbations per 6 Month Period before and after Treatment with Duodenal Substance*

PERIOD	BEFORE TREATMENT WITH DUODENAL SUBSTANCE						AFTER BEGINNING TREATMENT WITH DUODENAL SUBSTANCE					
	18 months		12 months		6 months		6 months		12 months		18 months	
Patients treated for 1½ years												
Number of patients.....	17		17		17		17		17		17	
Stool frequency:												
No. of patients.....	4	13	7	10	9	8	11	6	13	4	13	4
Stools per day.....	1-5	6-15	1-5	6-10	1-5	6-10	1-5	6-8	1-5	6-15	1-5	6-15
Exacerbations:												
No. of patients.....	2	13	2	14	4	12	12	4	11	6	13	4
No. of exacerbations.....	0	1	3	0	1	3	0	1	3	0	1	0
Patients treated for one year												
Number of patients.....	11		11		11		11		11			
Stool frequency:												
No. of patients.....	1	10	3	8	6	5	8	3	7	4		
Stools per day.....	1-5	6-15	1-5	6-15	1-5	6-15	1-5	6-10	1-5	6-8		
Exacerbations:												
No. of patients.....	1	8	2	9	5	6	8	3	8	3		
No. of exacerbations.....	0	1	2	0	1	2	0	1	0	1		

## OBSERVATIONS

The 28 patients are divided into two groups, one containing 17 patients who have been receiving the duodenal substance for 1½ years and a second group of 11 patients who have been under treatment for one year. All patients were given a diet low in residue, high in calories and high in vitamin content. No other specific medication was given during the period of treatment with duodenal substance with the few exceptions to be noted below. In Table 1 is presented the data on the number of stools per day and the number of exacerbations per 6 month period in these patients for the period of treatment and for a 1½ year period before treatment with duodenal substance. An exacerba-

tion was considered to have occurred when for three or more successive days the stools increased in frequency above 5 per day with blood in the feces and usually with abdominal discomfort. From the data in Table 1 it will be noted that both groups of patients had shown definite improvement under the regimens that were used in the period preceding treatment with duodenal substance. However when these treatments were stopped and duodenal substance was substituted for them the average degree of improvement was decidedly increased. Of the entire group of 28 patients, 17 had had an average of 6 to 15 stools a day for the 1½ year period before treatment with duodenal

TABLE 2

*Proctoscopic Evaluation of 28 Patients with Chronic Ulcerative Colitis before and One Year after Treatment with Duodenal Substance*

	BEFORE TREATMENT WITH DUODENAL SUBSTANCE				ONE YEAR AFTER TREATMENT WITH DUODENAL SUBSTANCE			
	1	2	3	4	1	2	3	4
Stages of pathology (according to Rankin et al.) . . . . .	0	2	14	12	0	7	16	5
Number of patients . . . . .								

TABLE 3

*Percentage of the 28 Patients in This Study Who Showed Various Criteria of Improvement during Treatment with Duodenal Substance*

CRITERION OF IMPROVEMENT	DECREASE IN NUMBER OF STOOLS PER DAY	DECREASE IN FREQUENCY OF EXACERBATIONS	GAIN IN BODY WEIGHT	DECREASE IN SEVERITY OF LESIONS SEEN PROCTOSCOPICALLY
Per cent of patients showing improvement . . . . .	60%	68%	70%	58%

substance. By the end of one year's treatment with duodenal substance 9 of these 17 patients were having less than 6 stools per day. Similarly the number of patients having at least one exacerbation per 6 month period was reduced from 21 out of 28 in the pre-treatment period to 7 out of 28 in the last 6 month period that this report covers.

Table 2 summarizes the proctoscopic findings immediately before beginning treatment with duodenal substance and one year after this therapy had been started. The classification of the four stages of severity outlined by Rankin, Bargen and Buie<sup>5</sup> is used. The number of patients with the most severe grade of lesions (grade 4) was reduced from 12 out of 28 to 5 out of 28 by the end of one year's treatment.

Table 3 summarizes the per cent of patients showing improvement according to each of 4 criteria, namely stool frequency, frequency of exacerbations, proc-

toscopic picture and change in body weight. Fifty-eight to 70 per cent of the patients showed improvement in each of the categories.

In those patients who were benefited by the treatment, improvement was first noted in from two weeks to two months after they began to take the tablets.

Three patients in addition to the 28 in the present series were started on treatment for brief periods but had to discontinue because of intolerance to the duodenal substance. In these individuals it appeared to cause an immediate aggravation of the condition. In addition to these three patients who showed an immediate unfavorable response to the duodenal substance, there were five patients in the group of 28 who apparently were unbenefited by the treatment. These patients were placed on sulfathalidine therapy during the acute exacerbations.

#### SUMMARY AND CONCLUSIONS

In 28 patients with chronic ulcerative colitis treated for 1 to 1½ years with a preparation of desiccated, defatted hog duodenum, the majority showed a decrease in the frequency of exacerbations.

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## THE PANCREAS

### CONTRIBUTIONS OF CLINICAL INTEREST MADE IN 1947\*

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The procedure used in summarizing knowledge in regard to the pancreas in 1947 is the same as that used in previous reviews. Only those contributions which contained objective information were selected. Those referring to the islet tissue were not included. Because of delay in the appearance of the Quarterly Cumulative Index, advantage was taken of the Current List of Medical Literature published monthly by the Army Medical Library, Washington, D.C. This permitted a somewhat earlier selection of the bibliography than would otherwise have been possible.

### CARCINOMA OF THE PANCREAS

A dismal report<sup>7</sup> describes the 6 year experience of a large clinic with 78 cases of carcinoma of the pancreas, duodenum and ampulla of vater. Sixty-five or 83 per cent of these patients were subjected to operation. Twenty-five had radical one stage or two stage resections with an operative mortality of 45 and 29 per cent respectively. Those surviving operation lived on the average 7 months, which was but 2 months longer than those who had a palliative operation. Moreover, those discharged alive following radical resection were in the hospital on an average of 60 days in comparison with 30 days for those who had a palliative operation. The latest information on the patient operated on by Whipple in 1940 indicates<sup>48</sup> that, although the patient is alive and comfortable 6 years after operation, he presents an enlarged nodular liver unquestionably due to metastases.

Nevertheless, successful, uncomplicated one stage radical resections continue to be recorded from various clinics, suggesting that the radical operation is gaining wider acceptance. For example, in one report<sup>11</sup> a 63 year old white male with pain of 2 weeks duration and weight loss for 6 months was operated upon and a carcinoma of the head of the pancreas resected. The patient was ambulatory on the second day and was well at 4 months, although still somewhat malnourished, and at 11 months was of normal weight and completely asymptomatic. In another patient<sup>20</sup> aged 78, a radical resection was successfully carried out 2 weeks after the onset of jaundice, and 4 weeks after the onset of abdominal pain and nausea. Of special interest in this case was the

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uncertainty of diagnosis at operation in spite of two biopsies, which revealed only fibrosis of the pancreas; the surgeon, nevertheless, decided to do a radical resection. The specimen subsequently showed adenocarcinoma deeply seated within the center of the tumor. Four months afterwards the patient was well and carrying on his normal activities.

In still another case report<sup>65</sup> a 69 year old woman was subjected to a one stage radical pancreatectomy after symptoms of jaundice and a 10 pound weight loss during 7 weeks, with practically no pain. In spite of the absence of pain, the patient at operation had stones in the gallbladder and common duct, and a carcinoma which involved the ampulla but extended into the common and pancreatic ducts and the head of the pancreas. The patient was completely well 18 months after operation.

Several unusual experiences have been described similar to previously reported observations illustrating the fact that carcinoma of the pancreas, especially in the body, does not always run true to form, but may present bizarre clinical and pathological features, making diagnosis difficult or impossible. For example, a case is described<sup>2</sup> in a 71 year old male who had epigastric pain for 6 weeks and a 15 pound weight loss, and in whom physical examination and a gastrointestinal series were completely negative. Death occurred on the 12th hospital day with unconsciousness, two generalized convulsions, and progressive coma. At autopsy a carcinoma of the body of the pancreas was found with many thromboses of the leg veins, pulmonary embolism and multiple infarctions. In another case<sup>43</sup> of a 76 year old man, those who saw him in three hospitalizations failed to arrive at the diagnosis which was made at autopsy. At the first admission only a hernia was found, although the patient complained of periumbilical pain of 2 months duration; the hernia was repaired. Six weeks later the patient was readmitted and a cholecystectomy and drainage of the common duct were carried out; stones and muddy material were removed from a dilated common duct. The third admission occurred shortly after discharge when the patient developed vomiting and became rapidly emaciated, and bile and pus were found emerging from the sinus in the right upper quadrant. A trans-duodenal drainage of the common duct was carried out 2 weeks later, which revealed no evidence of obstruction, although an abscess about the common duct was found and drained. However, the patient continued to go downhill, and cholangiograms through the T tube now revealed a distended common duct and definite evidence that there was an obstruction in the duodenum. At autopsy 18 days later there was an adenocarcinoma of the pancreas with extension into the neighboring structures and an ulceration of the stomach.

In still another patient,<sup>13</sup> a 51 year old housewife, there was anorexia and epigastric distension for 3½ months, jaundice for 3 weeks. A tremendous number of liver function tests were carried out, but all were normal. Neverthe-

less, operation was carried out and revealed adenocarcinoma with extensive liver metastases. Unlike most reported cases of carcinoma located in the head of the pancreas, the patient had no pain. An unusual presenting symptom was present in the case report<sup>39</sup> of a 68 year old man who had severe gross hematemesis and also exhibited occult blood in the stool. Because adequate blood replacement was ineffective, gastric ulcer was suspected and an exploratory laparotomy was carried out. However, there was no evidence of any lesion in the stomach or the first portion of the duodenum. A mass was felt through the duodenum which was biopsied and revealed carcinoma. A resection was successfully carried out 3 weeks later after adequate preparation. Examination of the specimen revealed that the mass was actually in the head of the pancreas. The patient was alive and in good health 6 months later. An interesting autopsy is described<sup>3</sup> in which widespread fat necroses were found in a patient with a highly differentiated acinous cell carcinoma of the head of the pancreas. Although widespread metastases were present, no tumor cells were found in these foci; nevertheless, the authors concluded that the tumor cells carried on the lipolytic function of the parent cell. The patient was a 56 year old white male who had complained merely of severe pain in both feet and hands and a weight loss of 35 pounds accompanied by anorexia and digestive malaise, fever, and periods of profuse sweating. Many nodules appeared in various parts of the body and he died on the 48th hospital day.

The importance of weight loss is suggested in the report<sup>27</sup> of a patient who presented this symptom plus cream colored, oily stools 3 to 4 times daily for a period of 4 months. Routine examination was negative. One month later evidence of diabetes appeared and the patient became jaundiced. A one stage resection of a large tumor of the head of the pancreas was carried out. The patient succumbed 10 months later; at autopsy there were local recurrences and liver metastasis.

Extensive pulmonary metastases from a carcinoma of the pancreas was reported in a 22 year old male<sup>64</sup> who presented signs of bronchial asthma. Because of epigastric pain, a widened duodenal curve after a barium meal, and an elevated serum amylase, the abdomen was explored and the diagnosis confirmed. Extensive metastases were seen; death occurred soon after and the tumor at autopsy had spread widely.

The diagnostic confusion between carcinoma of the body of the pancreas and psychosomatic disease is illustrated in the report of a case<sup>49</sup> of a 52 year old male with a 5 months history of pain with a 40 pound loss of body weight and anxiety. Complete physical and neurological examinations were negative. He was treated for 2 weeks as a psychogenic problem, and then was explored and a carcinoma of the body of the pancreas found, which was inoperable. Similar problems have been stressed in reports described in previous reviews.

The danger of a peptic ulcer following radical resections of the pancreas



was presented in a paper<sup>47</sup> in which 3 cases were described, one following total pancreatectomy, two following resection of the head and neck of the pancreas. In each case a perforated peptic ulcer was found distal to the anastomosis between the stomach and jejunum. In each case there was no pancreatic juice emptying into the jejunal loop. The author emphasizes the important point that in doing a radical resection of the pancreas the opening of the pancreatic and bile duct be made proximal to the gastrojejunostomy. The same complication of peptic ulcer with perforation and peritonitis was observed during experiments<sup>61</sup> performed on dogs with the objective of studying experimentally more radical procedures which might be applied to the treatment of patients with extensive carcinoma of the pancreas. In this study the portal vein was resected and implanted into the vena cava, a procedure which might be needed in extensive resections of the pancreas for carcinoma. The results, while disheartening, did illustrate many useful details which might be applied to further studies.

#### CYSTS OF THE PANCREAS

A number of cases have been described in 1947 of various types of cystic disease of the pancreas, most of them solitary or so-called pseudo cysts. However, an interesting study was made<sup>45</sup> of polycystic disease of the pancreas in a full term infant, who died 24 days later, with thorough serial sections which permitted the construction of a 3 dimensional model. A similar study was carried out in 2 other cases<sup>46</sup> from which the authors concluded that the sequence of anatomical changes was similar to those in polycystic disease of other organs. An unusual case of multilocular cysts of the pancreas is described<sup>25</sup> in which at operation the lesions were limited to the anterior aspect of the pancreas and successfully removed.

An unusually large number of solitary cysts have been reported during 1947; the largest series was a report<sup>14</sup> in which 6 patients were described. In one case the cyst was excised because it had produced common duct obstruction. In another the cyst cavity was infected and was drained; two others were also drained because of large vessels in the capsule. In one of the cases the cyst so simulated carcinoma that a radical resection was carried out; this was the only fatality in the group. Internal drainage by anastomosis was preferred by the author to external drainage and was successfully carried out in one case in which the cyst had obstructed the portal vein and caused numerous dilated blood vessels. The cyst was anastomosed to the common duct. Follow up of the 5 patients who survived operation showed that they were well 1 to 4 years afterwards. A solitary pancreatic cyst was found<sup>51</sup> in a 27 year old woman during the course of pregnancy, operation carried out at 4 months, and the cyst marsupialized to the skin after aspiration of 2

liters of thick, cloudy material. The cyst continued to drain for about 7 weeks and then closed firmly. The patient had a normal, spontaneous delivery and there was no recurrence. In another case<sup>10</sup> a pancreatic cyst was discovered 4 months postpartum, because of the appearance of a mass in the left hypochondrium. At operation the cyst was partially excised and the remainder anastomosed to the greater curvature of the stomach. Seven weeks after operation a barium meal revealed only a roughening at the area of the anastomosis. There were no symptoms at this time, but no later follow up was reported.

Various methods are still used in the operative therapy of pancreatic cysts and of the fistulas which are apt to follow external drainage. This is shown in numerous case reports. One author described 2 patients with pancreatic cysts,<sup>29</sup> one of them in a 63 year old male who remained well after simple drainage and marsupialization. In the second case, a 45 year old man, a fistula persisted into which a fibrosing agent was injected with satisfactory healing. The kind is not mentioned. Another author<sup>1</sup> described 2 cases, one a 61 year old white male with a large 2 liter pancreatic cyst which was marsupialized to the abdominal wall. A fistula persisted for 3 years; a second operation was carried out and the track, including a part of the pancreas, was removed, followed by a prompt recovery and no recurrence of the fistula during 2 year follow up. The second case was a 46 year old male in whom the cyst was also marsupialized. A fistula persisted for 2½ years, although the patient was asymptomatic otherwise. Two further cases are described by another author,<sup>41</sup> one of them a 42 year old male with an upper abdominal mass which, at operation, proved to be a pancreatic cyst which was marsupialized and was followed by prompt healing, with closure of the fistula at about 3 months. The second case presented symptoms of recurrent epigastric pain as well as a mass in the upper hypochondrium. At operation the cyst was also marsupialized, but the final result was not mentioned.

An unusual case was described<sup>68</sup> in a 26 year old alcoholic who complained of 50 pounds weight loss, left upper abdominal pain, nausea and vomiting and anorexia of one year's duration. Because of a mass which was palpated in the right hypochondrium, operation was carried out and a retroperitoneal cyst was found, the contents of which contained a high concentration of amylase. The walls of the cyst were marsupialized. After operation the track was irrigated with 2 per cent sodium salicylate and acetone. Skiodan was injected into the fistula and the entire pancreatic duct system was readily visualized. The fistula failed to heal and the patient was reported as dying elsewhere with jaundice and in coma. No autopsy was obtained. An interesting case was described<sup>35</sup> in a 29 year old woman who had been treated at many hospital admissions for a variety of complaints. Operation was carried out and a large

cyst found in the upper abdomen; it was anastomosed to a normal looking portion of the jejunum, and recovery was uneventful. There was insufficient evidence to determine whether this was a cyst of the spleen, pancreas or mesentery.

The traumatic origin of pancreatic cysts is illustrated in 2 case reports. One of them<sup>19</sup> was a 5 year old boy who fell while riding his bicycle. He was observed in the hospital because of abdominal pain, nausea and vomiting, and intermittent fever. Operation was performed on the 19th day after injury, and a cyst was found which distended the lesser peritoneal sac. It was aspirated and the wall excised. Recovery was entirely uneventful. The second case<sup>40</sup> was that of a 15 year old boy who was kicked in the upper abdomen and remained unconscious for 60 minutes. He was observed in a hospital and discharged 7 days later without specific therapy. Three weeks after this he was readmitted with recurrent severe abdominal pain and a 15 pound weight loss. Operation revealed a cystic mass in the mid portion of the body of the pancreas. Thirty cc. of bloody fluid was aspirated, and 380 cc. of free peritoneal fluid was found, which contained a high concentration of amylase. A drain was inserted into the cyst and sutured to the peritoneum. The wound drained for 26 days, and then the patient was discharged. Three months later the patient was again admitted because of recurrent symptoms and a definite mass in the appendiceal area. This was operated upon and 420 cc. of straw colored fluid found, which was not examined for its amylase content. The cyst was marsupialized and drainage ceased on the sixth day. Three months later another mass was palpated, this time in the epigastrium. There were no accompanying symptoms, and the mass subsided spontaneously. Ten months later the patient was reexamined and found to be entirely well with normal blood amylase and blood sugar.

Three cases of pancreatic cyst are described<sup>36</sup> in which a direct anastomosis was made between the cyst and the stomach or duodenum. All were successful, but the length of follow up was not stated.

#### ACUTE PANCREATITIS

The largest series of acute pancreatitis reported<sup>53</sup> contained details of 307 cases, although the basis for the diagnosis was not explained in all. There were 102 fatal cases and of these 85 were examined at postmortem. Of some interest was the fact that most of the patients with epigastric localization of pain were shown to have necrosis chiefly of the head of the pancreas, whereas those patients whose pain simulated coronary disease showed involvement of the tail of the pancreas. Only 20 per cent of the patients showed evidence of shock. No mention is made of amylase or lipase determinations in any of these cases. In another series of 10 cases<sup>34</sup> blood amylase tests were done in 4 and

found to be elevated. Operation was performed in 7 cases and of these 3 died; it is not clear whether these patients suffered from pancreatic necrosis. An interesting series of 3 cases is described<sup>31</sup> in which evidence was presented that there was an infection introduced in the body from the consumption of infected fish. Although the pancreas was definitely involved in an acute inflammatory process, it is clear that other organs were also involved. There were no studies of amylase or lipase in either the blood or urine.

Cholecystography during attacks of acute pancreatitis<sup>63</sup> in 10 patients failed to visualize the gallbladder; in 5 of these patients cholecystogram was repeated 5 to 14 days after the attack was over, and the gallbladder visualized normally. Exploratory operation was done on 5 patients and in 2 of these the gallbladder was removed but was found to be normal microscopically. No mention is made as to the basis upon which the diagnosis of acute pancreatitis was made, and particularly whether an elevation of serum amylase was found during the attack.

Successful operations in patients with acute pancreatitis have been described. In one of them<sup>60</sup> the patient had had attacks of pain with nausea and vomiting for one year. Operation was performed on the fifth hospital day after one such attack, and a distended gallbladder found with normal looking walls. The pancreas revealed definite induration and also a collection of fluid, which was present in the isthmus of the gland. It was punctured and found to contain 165 cc. of amber fluid, which was not tested for any pancreatic ferments. A cholecystostomy alone was carried out with an uneventful postoperative course. Eight months later the patient was well and asymptomatic.

In two cases the lesion was probably of the necrotic type.<sup>57</sup> One was a 39 year old man in whom at operation an abscess of the lesser peritoneal sac was found, the fluid showing definite evidence of tryptic activity. The urinary diastase was also elevated. Drainage resulted in an uneventful recovery. The second case was a 49 year old female who showed an elevated diastase and hyperglycemia. At operation, fat necrosis was evident and a large abscess was evacuated from the lesser peritoneal sac; the patient was entirely relieved of her symptoms and was entirely well 18 months later.

Another case of acute hemorrhagic necrosis of the pancreas<sup>22</sup> was that of a 39 year old obese male who entered the hospital with severe abdominal pain in the middle and lower part of the abdomen. He had had 3 similar attacks in 6 months. Because the patient did not recover under conservative therapy, he was operated upon one month later and free fluid was found in the peritoneal cavity, with extensive fat necrosis. Although the pancreas was not inspected, and no drainage of the lesser peritoneal sac was carried out, the patient had an uneventful recovery after a slow convalescence and about 3 months later was observed again and found to be completely well.

Support for non-operative therapy of acute pancreatitis is advanced in a not too detailed report<sup>29</sup> of 17 patients who were operated upon for an acute condition of the abdomen and hemorrhagic pancreatitis was found. All patients were drained and all died. This was during a period between 1920 and 1937. During this same period 3 patients, also with supposed hemorrhagic pancreatitis, were treated conservatively with 3 survivals. From 1938 to 1947, 18 cases were observed in which conservative non-operative therapy was carried out with only one death. As pointed out in previous reviews, inference from such comparisons lack validity because an anatomical diagnosis is uncertain from bedside observations alone. Thus the patients who were not operated on may have been suffering from interstitial pancreatitis, a lesion which is now known to subside spontaneously.

The mechanism of fat necrosis was studied<sup>50</sup> by injecting into the peritoneum a mixture of a solution of pancreatin and finally particulate graphite in 25 large white rats. At autopsy multiple areas of fat necrosis were found in both the abdominal and thoracic cavities, closely associated with the graphite delineated lymph channels. In support of the idea that the lymphatics transport lipase, the author also described a patient who died of pancreatitis on the third day after operation and in whom the disseminated fat necroses were distributed similarly to those in the rat, i.e., along the lymphatics. Thus the author believes that lipase transmitted by the lymphatic channels produces disseminated fat necrosis after injury or inflammation of the pancreas.

The treatment of pancreatic pain by lower dorsal sympathectomy is described<sup>65</sup> in 5 cases. The most dramatic results were obtained in a patient with recurrent pancreatitis associated with a calcified gland. In this case the operation was followed by sudden relief lasting over 6 months, in a patient whose pain could not be controlled even with heavy doses of narcotics taken over a period of 15 months before operation. The author emphasizes the diagnostic value of paravertebral block followed if necessary by splanchnic section in any patient with intractable upper abdominal pain of visceral origin.

In a short note, experiments are described without detail<sup>62</sup> in which in dogs pancreatic edema was observed to progress into pancreatic necrosis by temporarily blocking the upper pancreatic artery in the presence of edema.

#### SERUM AMYLASE

The value of serum amylase estimations has been well established by clinical study; yet many patients are still described with presumed acute pancreatitis in which this test was not carried out as routine. For example, in one study of 10 cases<sup>34</sup> blood amylase studies were made in only 4 of 10 cases, and in another series of 307 cases<sup>53</sup> it was not carried out at all. Reference has already been made to the finding of an elevated urinary amylase in cases of acute pan-

creatitis. No careful study has apparently been made in which urinary amylase changes have been correlated with those in the serum. If it should prove that urinary amylase is as consistently elevated and as closely connected with the clinical symptoms as the changes in the serum, it might be worth while substituting the more simple test in the urine for the one in the blood.

The possible value of an elevated serum amylase in the diagnosis of carcinoma of the pancreas is shown in one report<sup>64</sup> in which the value remained high during several weeks of observation, the diagnosis being confirmed at operation. On the other hand, another patient is described in whom symptoms were only of 4 weeks duration, and yet the serum amylase was reported as normal before operation. The danger of placing too much reliance on a slightly elevated serum amylase was illustrated in a case report<sup>59</sup> of a patient who had a slightly elevated value (180 with 120 as the upper limit of normal) with repeated attacks of epigastric and left upper abdominal pain. At operation the pancreas appeared normal as did all other intra-abdominal viscera. There was a tumor in the terminal area which was later reported to be a lymphosarcoma. The attacks of pain were obviously due to a partial intermittent intestinal obstruction and not to recurrent pancreatitis.

Elevations in serum amylase were observed<sup>62</sup> in a case of trauma to the pancreas. An 8 year old boy fell off his bicycle, striking his upper abdomen against the handle bars. Nine days later he was hospitalized because of increasing pain and fever, and the amylase was twice normal, later rising to 40 times normal and eventually falling to normal as symptoms subsided under conservative treatment. Except for upper abdominal tenderness and fever, examinations were negative including normal blood sugar.

#### ABERRANT PANCREAS

Four interesting cases of aberrant pancreas have been described. One of them<sup>16</sup> was in a 22 year old American Indian soldier who was operated upon for epigastric distress associated with massive gastric hemorrhage. A subtotal gastric resection was carried out and the aberrant pancreas was found in the stomach overlaid with tissues resembling Brunner's glands. There were 2 ulcerations of the gastric mucosa overlying the region, which was probably the site of the bleeding. The second case<sup>26</sup> was a 28 year old man who complained for one year of intermittent abdominal pain. X-ray revealed a Meckel's diverticulum which was found at operation and resected. In the gross there was evidence of a healed ulcer in the diverticulum. Examination showed an area of gastric mucosa at its tip, and an accessory pancreatic tissue in the wall. The postoperative course was uneventful. The third case<sup>12</sup> was a 29 year old male who complained of sudden severe abdominal pain and who was operated upon shortly afterwards with a diagnosis of perforated peptic ulcer. At oper-

ation an ileoileal intussusception was found and reduction was unsuccessful. The mass was therefore resected, an end to end anastomosis performed with an uneventful recovery. The specimen showed that the intussusception was due to a tumor in the wall of the ileum consisting of normal pancreatic acini without islet tissue. The fourth case<sup>5</sup> was a 6 year old white boy who complained of intermittent colicky abdominal pain associated with nausea and vomiting of 3 years duration, sometimes accompanied by fever up to 102 F. X-ray examination of the stomach revealed a small polyp about 1 cm. in diameter in the prepyloric portion of the stomach. At operation the polyp was found and had apparently caused symptoms by prolapsing through the pylorus and into the duodenum. This was excised and proved on microscopic section to contain pancreatic acini, without islets of Langerhans. The patient made an uneventful recovery.

#### PANCREATIC LITHIASIS

A large number of reports have appeared during 1947 regarding this condition. Although most of these reports in the past have indicated that pancreatic lithiasis is associated with fairly severe symptoms, one case is described<sup>80</sup> in which a definite calcification of the pancreas was found during the routine workup in a patient who had no specific clinical history except for mild symptoms resembling gallbladder disease. Moreover, the same author describes extensive calcification of the pancreas in a 41 year old farmer who had only epigastric pain and glycosuria which cleared up when the patient was placed on a simple diet. By contrast, pancreatic lithiasis produced a variety of severe abdominal manifestations<sup>69</sup> in a 33 year old white male with a history of 7 years of upper abdominal pain for which he had previously undergone appendectomy, cholecystectomy, operation for intestinal obstruction, gastroenterostomy and excision of a herniated intervertebral disc. He finally ended up with a diagnosis of constitutional psychopath. Complete study showed that the patient had a diffuse calcification of the pancreas, stool containing 42 per cent total fat and marked creatorrhea; pancreatic function tests showed an absence of trypsin in the duodenum. He was put on a low fat diet with vitamins A and D, and 90 grains of pancreatin daily. The stools dropped in number from 11 a day to only 2, and the patient gained 13 pounds. The same authors describe a second case in which pancreatic lithiasis was discovered only because of the x-ray findings. Analysis of the patient's hospital record showed that this diagnosis had never been made and that the patient was thought to be suffering from acute cholecystitis. He later died in a veteran's hospital, presumably of tuberculosis.

Resection of the pancreas for calcification has been carried out in several cases. In one report<sup>17</sup> a total pancreatectomy was carried out because of

severe pain. For the 4 weeks after operation during the hospital stay the diabetes was stable and easily controlled. Three months later the patient died at home from what the author believed was an unrecognized hypoglycemia. In another case<sup>54</sup> a 23 year old male with recurrent epigastric pain accompanied by nausea and vomiting of 3 years duration at intervals of 4 to 5 weeks, and lasting 4 to 5 days, was subjected to removal of the distal two-thirds of the pancreas, without producing any diabetes. The specimen revealed a few patches of normal pancreas with almost complete replacement of the rest with dense hyaline connective tissue containing numerous cysts and abscesses. Unfortunately, no follow up study was reported as to whether the patient was relieved of his symptoms. The same authors describe another case of calcification in a 55 year old male without mention of any therapeutic procedures. Severe pancreatic lithiasis which responded to surgical therapy was described<sup>58</sup> in a 35 year old male whose epigastric pain was aggravated by eating, and who for a while claimed to have taken 2 to 3 quarts of whiskey per day. X-ray of the abdomen revealed pancreatic calcification. At the first operation one of the pancreatic ducts was ligated and a portion of the body of the pancreas was removed; but this did not improve the symptoms, and during the next 7 years the patient became a morphine addict, taking as much as 20 grains in 24 hours. His stools were voluminous and fatty. A second operation was then carried out, and a transthoracic vagus resection and sympathectomy done from the thoracic 5 to lumbar 2 ganglion, including the greater, lesser and least splanchnic nerves and the celiac ganglion on the left side. Definite improvement followed this procedure, for during the following year, the patient was completely free of pain and gained 60 pounds with a complete return of his personality to normal so that he no longer took alcohol or narcotics. He was a diabetic, which was discovered on his first admission, and this was still present, but was completely controlled with adequate insulin intake. A less extensive procedure for the relief of pancreatic pain was described<sup>66</sup> consisting of bilateral splanchnic section in a number of patients with dramatic relief in at least one case of chronic recurrent pain apparently because of calcification of the pancreas. Without describing any of the clinical details, one report<sup>48</sup> mentions 5 partial and 2 total pancreatectomies for pancreatic lithiasis with 1 death.

#### PANCREATIC SECRETIONS

An extensive study of the pancreatic ferments obtained from the duodenal secretions was reported<sup>44</sup> in 36 patients upon whom 1000 tests were carried out. No secretin was used; olive oil was instilled into the duodenum as a pancreatic stimulant. The conclusions reached by the author were that a zero reading might be found in a normal patient at one examination, but not at subsequent examinations. On the other hand, in the presence of advanced and extensive



pancreatic disease, a zero reading was found consistently at subsequent determinations. Thus the author felt that it was necessary to repeat the tests in order to determine whether or not abnormal findings are significant. More consistent results have been obtained by those employing injections of secretin as the pancreatic stimulant; such studies have been reported in previous reviews. In another clinical study<sup>37</sup> the duodenal contents were studied in 3 patients after cholecystectomy in order to compare the secretions after the intravenous injection of secretin alone with that of secretin and morphine. Consistent findings were observed, indicating that morphine depresses the production of pancreatic enzymes. Thus, the volume of the duodenal juice was considerably diminished. The concentration of amylase and of trypsin was reduced to a fifth or a tenth of that found in the juice after secretin alone was injected. However, the bicarbonate concentration was little affected. Two of the 3 patients developed pain 5 and 30 minutes respectively after the injection of morphine. These findings confirm previous observations of the author in which the injection of morphine not only decreased sharply the secretion of pancreatic juice and bile to the duodenum, but also produced a rise in the serum pancreatic enzymes which the author believes is due to contraction of the sphincter of oddi.

Experiments on pancreatic secretions<sup>67</sup> in the dog have shown that the specific gravity and tryptic activity of the pancreatic juice secreted in response to continuous injections of secretin are increased following the administration of insulin. However, the average volume of the secretion during the first hour of the insulin was not significantly affected. The authors were unable to confirm the inhibitory effect on pancreatic secretion of hypoglycemia described in the literature, and explained this as being possibly due to anesthesia inasmuch as their animals were not anesthetized. A short abstract of experiments<sup>38</sup> on dogs is described in which peptic ulceration with histamine stimulation is increased by pancreatectomy or ligation of pancreatic ducts presumably because of the removal of the protective action of pancreatic juice. Peptic ulcers following resection of the pancreas have already been mentioned.<sup>472,61</sup> In another brief abstract<sup>32</sup> the amount of pancreatic secretion was found to be greatly diminished following gastric resection in the dog, particularly when a long, efferent duodeno-jejunal loop was used. A cytochemical study of phosphatases was carried out<sup>21</sup> and the pancreas of the rat and monkey found to contain no phosphatase. Histological examination of the pancreas<sup>4</sup> in patients dying of uremia showed, among other things, varying degrees of acinar dilation, flattening of cells and inspissation of secretions, but no duct obstruction.

Several additional methods have been described for the study of pancreatic secretion. In one of them<sup>6</sup> a special *T* shaped metal cannula is used which permits selective removal of pancreatic juice or its automatic return to the

intestinal tract. In another report<sup>33</sup> a simple method for the preservation of an open pancreatic fistula in the dog was described in which the animals were maintained on trays of clean white sand which apparently absorbs the secretion so rapidly that no changes occur in the tissues about the wound. The daily ration for such a dog is also described. Animals were maintained from 3 months to 2½ years without difficulty. An ingenious method<sup>24</sup> is described whereby a portion of the intact pancreas may be observed in a transparent chamber attached to an incision in the abdominal wall of the living unanesthetized mouse.

Pancreatectomy was found to have an interesting influence on the plasma-prothrombin.<sup>9</sup> In 4 completely pancreatectomized dogs maintained on insulin there is a fall in the prothrombin value of moderate degree for about a week, and then definitely subnormal values. This low value was so little affected by the administration of vitamin K that the authors assume that the pancreas, while not essential for the formation of prothrombin, contributes something to the body which enables the liver to manufacture this enzyme. In other words, disease or removal of the pancreas presumably leads to a fall in prothrombin by compromising this functional capacity of the liver.

#### *Common Channel*

Although it is generally agreed that the pancreatic and common ducts may form a common channel in at least half of normal adults, 3 further studies concerning this relationship have appeared. An anatomical study<sup>28</sup> was made of 150 fresh, unfixed specimens consisting of the pancreas, duodenum and common bile ducts removed intact at autopsy. An anatomical possibility for the formation of a common channel at the ampulla of Vater is listed in at least 50 per cent of these specimens. In a clinical study of 5 cases with common duct drainage<sup>23</sup> amylase was recovered in the bile in each case. Moreover, the pancreatic duct was visualized when iodized oil was injected into the common duct. The resistance of the sphincter of Oddi was measured under normal conditions and found to be 150 mm. of water, whereas 2 minutes after the subcutaneous injection of one-sixth grain of morphine, the sphincter resistance rose to 300 mm. of water. Interduodenal installation of 20 cc. of tenth normal hydrochloric acid caused an immediate spasm with a rise of the sphincter resistance from 150 to 250 mm. of water, the effect wearing off in about 10 minutes. When pancreatic secretin was given intravenously and bile from the common duct was collected, amylase was found only in the specimens removed at 10 and 20 minutes after the injection. However, when morphine was given before the injection of secretin, no amylase was recovered. On the other hand, when 20 cc. of tenth normal hydrochloric acid was instilled into the duodenum, the greatest amount of amylase was recovered from the biliary drainage. From

his studies the author calculated that from one-third to one-half of the total amount of pancreatic juice could pass up the common bile duct. Other physiological tests of great interest were carried out in these patients. It is clear that this approach to the problem of the common channel and its relationship to clinical symptoms is a good one and further information is awaited.

Two clinical cases were presented showing that a common channel undoubtedly exists.<sup>18</sup> In one patient following cholecystectomy for recurrent pain, biopsy of a hard, indurated pancreas showed definite biliary deposits in the tissue, which the author explained as having reached there through a junction of the lower end of the common duct and the pancreatic duct. The second case was that of a 60 year old female in whom after cholecystectomy and common duct drainage, pancreatic ferments were demonstrated in the bile.

### *Lipotropic Factors*

Three interesting studies have appeared regarding the lipotropic factors in the pancreas. The influence of methionine was studied<sup>15</sup> in completely depancreatized dogs maintained with insulin. In the first series of experiments it was shown that while unhydrolyzed protein did not prevent the development of fatty liver, hydrolyzed protein did so. However, when 0.6 of a gram of free methionine was fed, the fatty liver was prevented just as effectively as 20 grams of hydrolyzed protein. The author therefore believes that sufficient free methionine must be available in order to exert a lipotropic effect, and that whole protein is not effective because its methionine content is not immediately available for such a purpose. That the pancreatic juice is a rich source of the lipotropic factors in depancreatized dogs maintained with insulin is shown in observations of 17 animals<sup>42</sup> in whom the daily ingestion of as little as 10 cc. was sufficient to keep the liver normal in regard to their total fatty acid content for as long as 5 months. In 5 other animals a drop in the plasma choline was established and then 50 cc. of pancreatic juice added to the feeding, followed by a rapid rise in the low value of plasma choline in all cases. Pancreatic juice was then discontinued and the plasma choline levels fell again to low values.

### *Pancreatin*

It is hard to understand the rationale by which pancreatin was employed for the treatment of roentgen sickness, but 12 cases are reported<sup>56</sup> in which three 10 grain gelatin-coated capsules of pancreatin taken with a full glass of water before each meal had a definitely beneficial effect on nausea. In view of the variations in the potency of pancreatic preparations, a report is of interest<sup>8</sup> in which the tests used for measuring the lipolytic activity of various preparations are scrutinized, and recommendations for making the assay more accurate.

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## "CHRONIC GASTRITIS"

### A STUDY OF THE RELATION BETWEEN MUCOSAL CHANGES AND SYMPTOMS

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The development of the flexible gastroscope by Schindler in 1932 enabled for the first time the *in vivo* study of the appearance of the gastric mucosa in man. Important contributions subsequently were made by Schindler,<sup>1, 2</sup> Moutier,<sup>3</sup> Faber,<sup>4, 5</sup> Henning,<sup>6</sup> Gutzeit<sup>7</sup> and others. However, the relationship of various changes in the appearance of the gastric mucosa to the symptoms of the patient remains a matter of controversy. To obtain further information on this subject, a comparison was made of the incidence of symptoms among patients with a gastroscopically abnormal mucosa and among 100 individuals with symptoms but in whom the mucosa appeared normal.

#### PRESENT STUDY

The patients selected for this study were free of organic disease of the gastrointestinal tract, as indicated by complete physical, laboratory and roentgenologic examinations. Four groups were analyzed: a) 100 patients in whom the gastric mucosa appeared entirely normal gastroscopically; b) 50 patients with "atrophic gastritis" (grayness and visible blood vessels); c) 50 patients with "chronic superficial gastritis" (edema, erythema and adherent exudate); and d) 50 patients with "hypertrophic gastritis" (irregular, nodular, cobblestone-like mucosa). The incidence of symptoms in these groups is shown in Table 1.

It will be noted that patients with atrophy and with "superficial" changes complained twice as frequently of flatulence and half as often of epigastric distress as did those with a cobblestone-like or normal appearing mucosa; otherwise, the incidence of symptoms was essentially the same in the four groups.

The duration of symptoms was not significantly different in the four groups (Table 2). The diagnosis of irritable colon or psychoneurosis was made with similar frequency in all four groups.

#### DISCUSSION

The interpretation of symptoms referred to the epigastrium in patients with no roentgenologic evidence of organic disease has perplexed and fascinated many investigators. In the past the symptoms have been erroneously related to such hypothetical clinical entities as "hyperchlorhydria," "dyspepsia,"

"ptosis," "chronic cholecystitis," "chronic appendicitis," etc. In recent years<sup>1, 2, 9, 10, 11</sup> the symptoms frequently have been attributed to changes in the appearance of the gastric mucosa. This problem has been discussed by numerous authors.<sup>1-27</sup> The present study demonstrates a lack of correlation

TABLE 1  
*Symptoms and Changes in Appearance of Gastric Mucosa*

SYMPTOMS	GASTROSCOPIC DIAGNOSIS			
	Normal	"Atrophic Gastritis"	"Superficial Gastritis"	"Hypertrophic Gastritis"
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Pain in epigastrium.....	40	32	34	34
Epigastrium distress.....	30	16	12	30
Diffuse abdominal pain.....	4	2	10	2
Flatulence.....	14	32	44	14
"Heartburn".....	3	12	12	10
Anorexia.....	6	4	4	6
Loss of weight.....	11	16	26	14
Nausea.....	11	16	16	18
Vomiting.....	13	10	12	10
Weakness, fatigue.....	19	16	12	10
"Nervousness".....	8	10	10	14
Dizziness.....	6	10	4	4
Insomnia.....	3	4	4	4
Constipation.....	12	10	6	14
Diarrhea.....	10	10	18	12

TABLE 2  
*Duration of Symptoms and Changes in Appearance of Gastric Mucosa*

DURATION OF SYMPTOMS	GASTROSCOPIC DIAGNOSIS			
	Normal	"Atrophic Gastritis"	"Superficial Gastritis"	"Hypertrophic Gastritis"
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
1 day to 6 months	13	22	16	24
6 months to 1 year	13	14	22	16
1 year to 2 years	14	12	18	10
2 years to 4 years	15	18	10	10
4 years to 6 years	12	10	10	9
6 years to 10 years	11	8	2	10
10 years to 15 years	7	4	4	4
More than 15 years	7	2	10	8
Not well determined	8	10	6	10

between any particular symptom or group of symptoms, and any particular type of mucosal change. No difference was found in the duration of symptoms in each group. These findings are in agreement with the observations of Henning,<sup>6</sup> Ruffin<sup>20</sup> and others.<sup>3, 24, 27</sup>

# SUMMARY

The incidence of symptoms in individuals without roentgenologic evidence of disease and with a gastroscopically normal mucosa does not differ significantly from that observed in patients with "atrophic gastritis" (atrophy), "chronic superficial gastritis" (erythema, edema, exudate), and "hypertrophic gastritis" (cobblestone-appearing mucosa).

It is entirely possible, however, that in individual cases the gastrointestinal symptoms may be attributable to erosive and inflammatory processes in the mucosa.

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## TURBIDIMETRIC ESTIMATION OF SERUM COLLOIDS IN THE DIFFERENTIAL DIAGNOSIS OF HEPATOBILIARY DISEASE

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Disturbances in serum protein relationships have been recognized in diseases of the liver for a number of years.<sup>1-8</sup> Although the mechanisms responsible for these changes have not been clarified, many laboratory procedures for the clinical evaluation of hepatic damage have been based on the rearrangement of serum protein noted in hepatic cirrhosis, infectious hepatitis and to a more variable degree in metastatic disease of the liver.<sup>2, 4</sup> Among such tests may be mentioned the Takata-Ara reaction,<sup>9, 10</sup> the formol-gel reaction,<sup>11</sup> colloidal gold and colloidal red tests,<sup>12</sup> the cephalin-cholesterol flocculation test,<sup>9, 13, 14</sup> and the thymol turbidity reactions.<sup>4, 15-19</sup>

These procedures are subject to two general disadvantages:

1. They involve a number of constituents of serum, each of which may be subject to individual variation. It is known<sup>4, 16-18</sup> that the thymol turbidity reaction is based on precipitation of the several globulin fractions, together with one or more serum lipids (or lipoproteins) and thymol. This test is further subject to influence by variations in serum albumin. The numerous variables bearing upon this group of tests have been discussed by Neeffe and his associates,<sup>12</sup> by Kunkel and Hoagland,<sup>4</sup> and by others.<sup>6, 7, 16, 18-20</sup> The influence of these variables is reflected in a lack of specificity, and some losses in validity, in the application of these tests to clinical practice.

2. The reagents employed in these procedures are difficult of preparation, unstable and difficult of reproduction.<sup>9, 17</sup> These factors introduce additional possibilities of error and magnify the problem of the adaptation of the tests to the routine clinical laboratory.

A simple yet accurate procedure, employing stable, reproducible reagents is needed for the evaluation of a single constituent of serum, the concentration of which is known to be altered in hepatic disease. In the search for such a test, it has been considered that serum gamma globulin offers many features desirable in an assay objective: (1) the alterations in serum protein occurring in liver disease seem most specifically related to the gamma globulin fraction;<sup>1, 2</sup>

(2) electrophoretic studies have shown the gamma globulin fraction to be free from the lipid and lipoprotein known to migrate with the beta globulin fraction;<sup>21, 22</sup> and (3) concentration of gamma globulin in the serum may be significantly altered without recognizable changes in total protein, total globulin, or albumin-globulin ratios as these are commonly determined.<sup>1</sup>

Kunkel<sup>3</sup> has recently described a rapid turbidimetric procedure for the estimation of gamma globulin in serum. His method is based on the principle of precipitating gamma globulin as a finely turbid suspension by high dilution of serum in solution of zinc sulfate of low-ionic strength, buffered with barbital and sodium barbital to a pH of approximately 7.4. Turbidity values are expressed in arbitrary units, based on the comparative turbidity of a standard suspension of barium sulfate similar to that employed for the estimation of thymol turbidity. By electrophoretic migration and other studies, Kunkel has been able to show that the precipitates so obtained consist chiefly, though not entirely, of gamma globulin. Variations in serum lipid or in serum albumin are not factors which interfere significantly.

Kunkel's original studies indicated a range of 2 to 8 units of gamma globulin in normal serums as indicated by turbidimetric means. High turbidimetric values of gamma globulin were found in cases of infectious hepatitis, hepatic cirrhosis, and other states associated with hypergammaglobulinemia. In infectious hepatitis, increase in the turbidimetric values of gamma globulin in the serum tends to follow a positive thymol turbidity reaction, and to continue after the thymol turbidity reaction has returned to normal. His findings in hepatic cirrhosis speak for a lower incidence of normal values of gamma globulin in this condition than the thymol turbidity technic has indicated.<sup>6, 7, 12, 15, 17, 19, 20</sup>

These studies have led us to investigate the adaptability of the turbidimetric estimation of gamma globulin to the differential diagnosis of hepatobiliary disease. We are reporting herein our findings in the serums of normal subjects, of patients with infectious hepatitis, hepatic cirrhosis, cholecystitis or obstructive jaundice, and of a miscellaneous hospital population. Our results support the use of this test procedure in the differential diagnosis of hepatobiliary disease.

#### MATERIAL

Subjects whose serum samples were studied in this investigation and the tests performed on them are indicated in Table 1.

Donors to the blood bank were selected as a group who were fairly representative of the healthy adult population of the Rochester area. The addition of a second group of donors was made necessary by our later inclusion in the study of a procedure for turbidimetrically estimating the concentration of total serum lipids as described to us by Kunkel.<sup>23</sup>

In our miscellaneous hospital group we included hospitalized patients whose

illnesses, in so far as could be ascertained, were not related to the hepatobiliary system, or to other conditions known to affect serum gamma globulin. This group serves as a second control group and offers a comparison between healthy subjects, and the so-called hospital normal classification. In our early review of this grouping, we were led to place patients who had peptic ulcer in a separate category, due to the consistently low turbidimetric readings obtained on serum samples.

Since we were using the serum of patients to evaluate a new procedure, we established the diagnostic classification on the best available clinical and laboratory criteria. In the majority of cases, the clinical diagnosis was supported by the findings at biopsy, necropsy or surgical examination, and we

TABLE 1  
*Distribution of Subjects Studied*

DIAGNOSTIC CLASSIFICATION	TOTAL CASES	TURBIDITY TESTS EMPLOYED, CASES		
		Gamma globulin	Thymol	Total lipids
Blood bank donors:				
Group 1.....	136	136	136	
Group 2.....	100	100	100	100
Miscellaneous hospital population.....	115	115	108	77
Peptic ulcer.....	64	64	62	38
Infectious hepatitis.....	16	16	16	9
Hepatic cirrhosis.....	33	33	32	23
Cholecystitis.....	33	33	33	20
Obstructive jaundice:				
Malignant basis.....	12	12	12	9
Benign basis.....	50	50	49	35

fully considered the results of other laboratory tests as performed in the laboratories of the Mayo Clinic in our disposition of the patients in the various groups.

#### METHODS

Turbidimetric estimations of serum gamma globulin were made by the method of Kunkel,<sup>3</sup> with values expressed in units, based upon the barium sulfate standard described by this author. Values for thymol turbidity were determined by the method of MacLagan,<sup>16</sup> as adapted to the Coleman Jr. spectrophotometer by Shank and Hoagland. We have retained the barium sulfate standard used in the modification of Shank and Hoagland,<sup>18</sup> in preference to the more dilute suspension employed by Kunkel.<sup>15</sup> Values of gamma globulin by this procedure in normal serums are considered to range from 0 to 5 units. Values for total lipids in serum have been estimated turbidimetrically by the procedure described to us by Kunkel. These values have been expressed in

milligrams per 100 cc. by the use of conversion tables furnished us by this investigator.

Studies were made on the samples of serum on the day the blood was drawn, since we found some inconstant loss of turbidity values in samples analyzed on successive days. Three tubes were prepared for each sample. Into these were measured, respectively, 3 cc. of thymol buffer,\* 3 cc. of zinc sulfate buffer,† and 1.8 cc. of Kunkel's salt-phenol reagent for total lipids‡. A 0.2 cc. pipet, graduated to 0.001 cc., was used to convey successively 0.05 cc., 0.05 cc. and 0.1 cc. of serum to this set of tubes. The final dilution of serum was thus 1:60 for the gamma globulin turbidity and the thymol turbidity tests, and 1:18 for the total lipid turbidity estimations. The contents of the tubes were thoroughly agitated, allowed to stand for thirty minutes, again thoroughly mixed, and results were read in standard cuvettes on the optical density scale of the Coleman Jr. spectrophotometer. The appropriate reagent was used as a blank for each series of readings. Interference due to the yellow color of bilirubin in jaundiced serums was minimized by the use of light transmitted in the red band at 650 millimicrons.

## RESULTS

### *Normal Groups*

Our findings in the several groups of normal persons previously described are given in Table 2, and depicted graphically in Figure 1.

Differences in mean values for thymol turbidity and for gamma globulin turbidity observed in the two donor groups are not considered statistically significant. It is evident, therefore, that for 236 blood bank donors, mean values for gamma globulin turbidity were approximately 11 units and for thymol turbidity slightly less than 2 units.

The mean value of 678 mg. per 100 cc. for total lipids noted in the donor group 2 is higher than the range of normal established by the clinic laboratories

\* To facilitate comparison of results, our thymol buffer was taken from lots prepared and checked for use in the clinic laboratories by Dr. F. D. Mann, by the procedure of MacLagan.<sup>16</sup>

† Zinc sulfate buffer of Kunkel<sup>3</sup>:

ZnSO <sub>4</sub> ·7H <sub>2</sub> O.....	24 mg.
Barbital.....	280 mg.
Sodium barbital.....	210 mg.
Distilled water to make.....	1 liter.

Each new lot of buffer was checked against the previous lot on identical serums before use in analysis. We have experienced no difficulties in thus reproducing this reagent.

‡ Salt-phenol reagent of Kunkel:

Liquefied phenol.....	1.0 cc.
Sodium chloride.....	12.0 gm.
Distilled water to make.....	100.0 cc.

Each lot of this reagent was checked against the preceding lot before use in analysis. As advised by Kunkel, we refrigerated this reagent when not in use.

TABLE 2  
Results of Turbidimetric Analyses in Control Groups

DIAGNOSIS	DETERMINATIONS	CASES	RESULTS, UNITS			
			Mean	Standard deviation	Range	Significance of difference from donor group 1
Blood bank donors: Group 1	Gamma globulin	136	11.2	2.7	4.0-18.0	
	Thymol turbidity	136	1.9	0.79	0.4- 5.0	
Group 2	Gamma globulin	100	10.7	1.8	5.6-19.0	$P^* < 0.1$
	Thymol turbidity	100	1.9	0.69	0.5- 4.0	$P = 0.75$
	Total lipids	100	678 mg.†	104	480-900 mg.†	
Miscellaneous hos- pital population	Gamma globulin	115	9.4	3.4	3.0-25.0	$P < 0.01$
	Thymol turbidity	108	2.0	0.88	0.6- 5.2	$P = 0.45$
	Total lipids	77	643 mg.†	159	405-1,250 mg.†	$P < 0.1†$
Peptic ulcer	Gamma globulin	64	8.8	3.02	5.0-20.0	$P < 0.01$
	Thymol turbidity	62	1.7	0.73	0.7- 4.6	$P = 0.04$
	Total lipids	38	658 mg.†	166	465-1,070 mg.†	$P = 0.45†$

\* Values for P of less than 0.05 are generally considered significant.

† Milligrams per 100 cc. of serum.

‡ Compared with group 2.

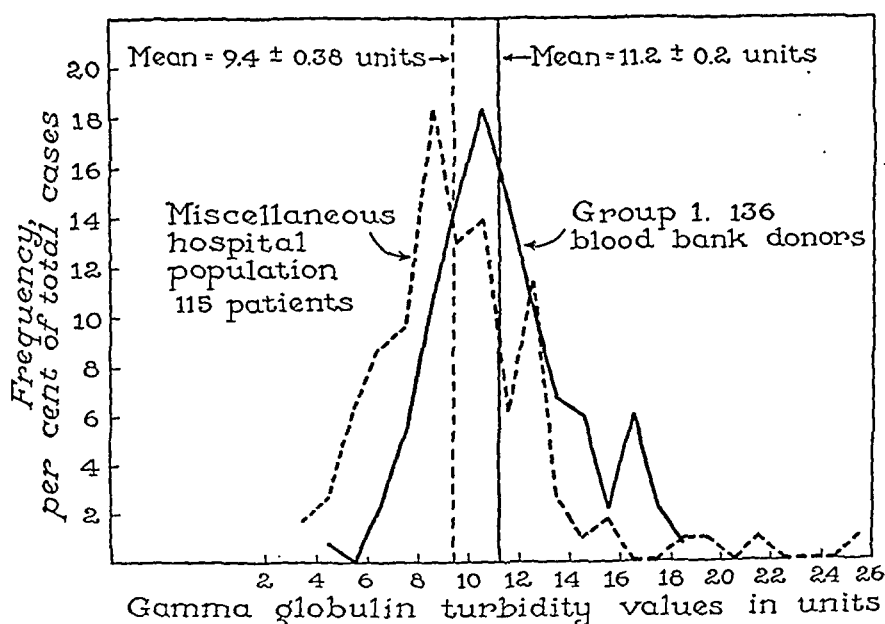


FIG. 1. Distribution curves of two control groups.

using chemical procedures (400 to 650 mg. per 100 cc.). Our turbidimetric values for total lipids have been about 10 to 15 per cent higher than the clinic laboratory reports on the same samples.

Distribution curves for gamma globulin turbidity and for thymol turbidity (Figs. 1 and 2) differ from the expected normal configuration only in a slight skewing at the extreme right end of the curve; that is, in the higher range of values. A similar deviation was noted by Trevorrow and co-workers<sup>24</sup> in their extensive study of total globulin values in 260 normal persons more than five years of age. These authors ascribe this deviation to the possibility of including in normal adult groups a few persons whose globulins have been elevated by a

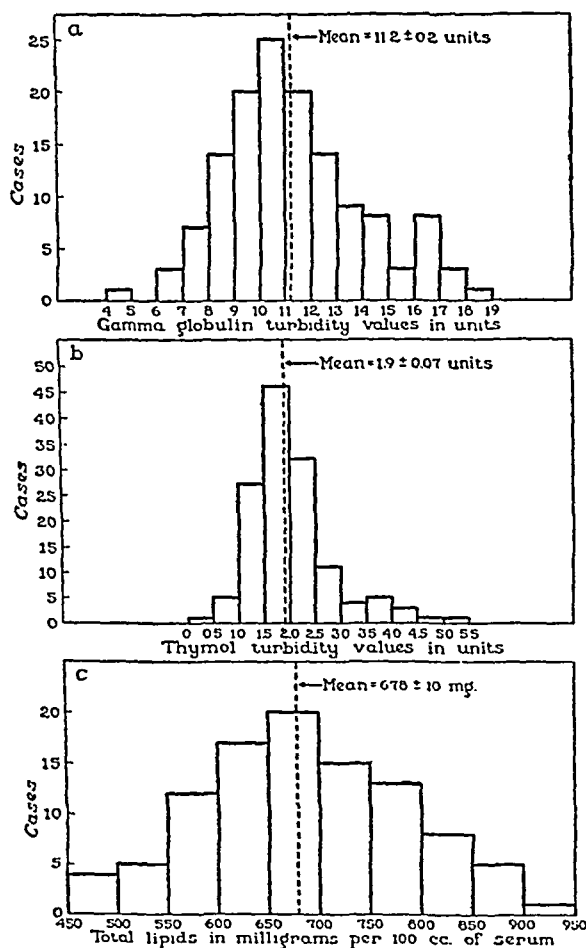


FIG. 2. Results of tests on serum of 136 donors to blood bank (group 1): *a*, gamma globulin turbidity test; *b*, thymol turbidity test; *c*, total lipid.

past infection or immunization. Some support for this hypothesis may be gained from our Figure 2, in that skewing to the right is not to be seen in the distribution curve of values for total lipid.

It may be concluded from Table 2 that turbidimetric values for gamma globulin are significantly lower in the miscellaneous hospital population than in the donor groups ( $P < 0.01$ ). This difference is graphically depicted in the widely distorted distribution curve for these values, shown in Figure 1. Tur-

bidimetric values for gamma globulin in the peptic ulcer group show an even greater difference from the values in the donor groups. Krebs<sup>25</sup> has shown that hypogammaglobulinemia may be a result of malnutrition and inadequate intake of protein.

Differences in values for thymol turbidity between donor groups and the miscellaneous hospital population are not considered significant. However, a mean value for the peptic ulcer group is significantly lower than the normal mean in the donor groups ( $P = 0.04$ ). All observed values were within the generally accepted normal range of 0 to 5 units, however.

No significant differences in mean total lipid turbidity were found on comparing the miscellaneous hospital population and the peptic ulcer groups with the donor group 2.

Our values for gamma globulin turbidity are somewhat higher than Kunkel's,<sup>23</sup> although we have been able to duplicate his values on a sample of serum supplied us from his laboratory. We agree with him that such differences are most probably due to variations in the preparation of standard suspensions of barium sulfate. On this basis, we suggest that each laboratory establish an individual basis of normal values for the evaluation of clinical subjects.

### *Clinical Conditions*

Results of our studies in the groups of various types of conditions previously described are summarized in Table 3. By means of scatter graphs (Fig. 3) we have depicted the spread of results within the individual groups. Each point on these figures represents an individual patient, or the highest of several values obtained in several samples from the individual. On these graphs, horizontal solid lines indicate the mean value in donor group 1, and values of two times the standard deviation above and below this mean are indicated by the broken lines. We believe this manner of indicating normal variation facilitates comparison of normal and patient groups, and further affords a comparison of diagnostic efficiency between the gamma globulin and the thymol turbidity procedures.

High percentages of positive values for both gamma globulin turbidity and thymol turbidity in infectious hepatitis and in hepatic cirrhosis are evident in Table 3 and Figure 3. In sharp contrast, the majority of the values in cases of cholecystitis and in obstructive jaundice, are within the range of normal mean plus or minus two times the standard deviation. From Figure 3 it will be seen that values for total lipids in the serum do not exhibit this constancy of difference between intrahepatic and posthepatic diseases. A tendency toward high values for total lipids in obstructive jaundice is in accord with expectation. Our findings in infectious hepatitis may be altered with

**TABLE 3**  
*Summary of Results of Turbidimetric Analyses in Hepatobiliary Disease*

DIAGNOSIS	DETERMINATIONS	CASES	RESULTS, UNITS	
			Mean	Range
Infectious hepatitis	Gamma globulin	16	33.6	15.6-72.0
	Thymol turbidity	16	9.5	3.8-15.5
	Total lipids	9	706 mg.*	480-1,150 mg.*
Hepatic cirrhosis	Gamma globulin	33	27.9	13.4-45.8
	Thymol turbidity	32	5.92	1.6-13.0
	Total lipids	23	722.2 mg.*	450-1,490 mg.*
Cholecystitis	Gamma globulin	33	10.39	5.0-19.2
	Thymol turbidity	33	1.93	1.0- 3.5
	Total lipids	20	619 mg.*	460-880 mg.*
Obstructive jaundice: malignant basis	Gamma globulin	12	13.0	7.2-20.0
	Thymol turbidity	12	3.23	1.6- 6.0
	Total lipids	9	1,242 mg.*	790-2,050 mg.*
Obstructive jaundice: benign basis	Gamma globulin	50	11.18	4.4-24.0
	Thymol turbidity	49	2.8	1.0- 6.0
	Total lipids	35	936 mg.*	475-1,975 mg.*

\* Milligrams per 100 cc. of serum.

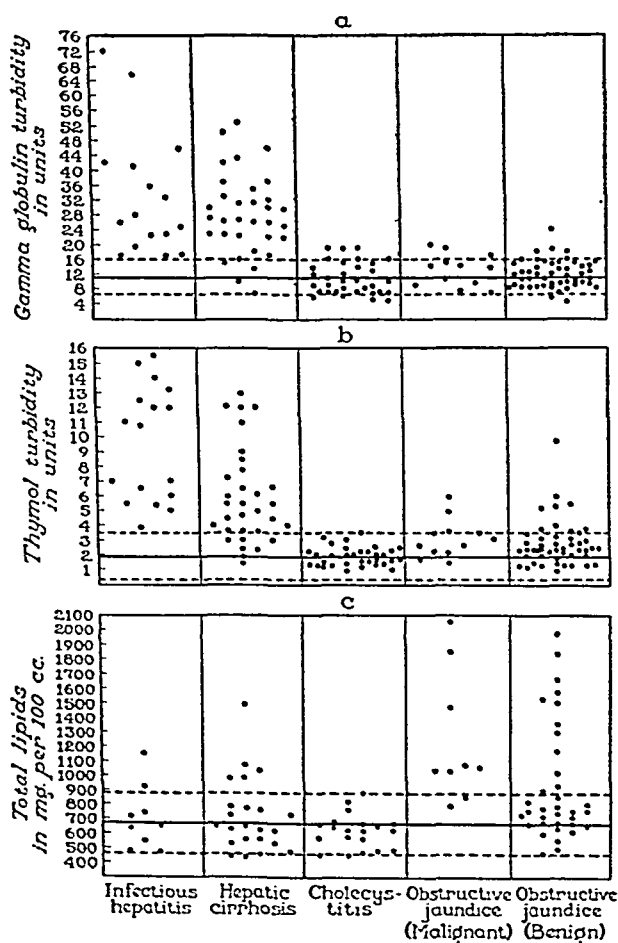


FIG. 3. Results of tests on serum in cases of hepatobiliary disease: a, gamma globulin turbidity test; b, thymol turbidity test; c, estimation of total lipid.



respect to total lipids as more data are obtained. It is known<sup>4, 20</sup> that serum lipids frequently are elevated in the early stages of infectious hepatitis, followed by a fall to normal as the gamma globulin values begin to rise. Elevated values for total lipids were obtained in 5 of 23 cases of hepatic cirrhosis studied in our series.

In agreement with the discussions of Magath<sup>26</sup> and of Mann and associates,<sup>17</sup> we have felt that a good index of efficiency of a laboratory test is provided by the percentage of positivity in cases of known diagnosis, as contrasted with groups considered to be normal. On this basis, we have compared the thymol turbidity and gamma globulin turbidity reactions as indicated in Table 4.

If we accept the mean value of the normal groups plus two times the standard deviation as a basis for such comparison, then the upper limits of normal become 16.6 units and 3.5 units for gamma globulin turbidity and thymol turbidity respectively. On this basis, there is a somewhat lower incidence of positive values in donor groups 1 and 2 for gamma globulin turbidity than for thymol turbidity (3.0 per cent and 4.6 per cent respectively); a higher incidence of positive values in hepatic cirrhosis (82 per cent and 75 per cent); and a lower incidence of positive values in obstructive jaundice due to malignancy (17 per cent and 42 per cent), or to benign conditions (4 per cent and 22.5 per cent). The results of the two tests appear to be of approximately equal value in infectious hepatitis and in cholecystitis.

If we consider the conventional upper limit of normal for thymol turbidity of 5 units, then 15 of 32 cirrhotics (47 per cent) would be considered to have normal values. The somewhat higher diagnostic efficiency of the gamma globulin turbidity test may be related to the experimental finding that the characteristic protein changes in cirrhosis occur in the gamma globulin fraction.<sup>1</sup> The higher incidence of positive values for thymol turbidity than for gamma globulin turbidity in obstructive jaundice may be related in part to the tendency toward higher lipid values in this group, and the known influence of serum lipid on the thymol turbidity reaction as previously indicated.

These considerations indicate for the gamma globulin turbidity test a somewhat higher diagnostic efficiency in the differentiation of intrahepatic and posthepatic disease than has been our experience with the thymol turbidity test.

Ten patients in our group who had hepatic cirrhosis were considered to have alcoholism as a prominent etiologic factor. Values for gamma globulin within this subgroup ranged from 13.4 to 29.2 units, with a mean of 22.7 units. These figures may be compared with a range of 13.4 to 45.8 units, and a mean of 27.9 units for the entire group of cirrhotic patients. Two of the 10 patients had gamma globulin turbidity values below the value of normal mean plus two times the standard deviation. Thymol turbidity values for the 10 cases of

presumed alcoholic cirrhosis ranged from 1.9 to 8.5 units, with a mean of 4.5 units, as compared to a range of 1.6 to 13.0 units and a mean of 5.9 units for the entire group. In 7 of these 10 cases, values were less than the accepted normal limit of 5 units, and in 3 were less than the upper limit of normal as we have defined it for comparison.

These figures indicate that values for both gamma globulin and thymol turbidity are somewhat lower and more variable in alcoholic cirrhosis than in cirrhosis due to other causes. Similar findings for the thymol turbidity reaction were reported by Mann and associates.<sup>17</sup> Our data indicate a higher incidence

TABLE 4

*Comparison of Diagnostic Efficiency of the Gamma Globulin and Thymol Turbidity Estimations*

DIAGNOSIS	CASES	DETERMINATION	VALUES NORMAL MEAN S.D. +2.0		REMARKS
			Cases	Per cent	
Normal donor groups 1 and 2	236	Gamma globulin	7	3.0	Highest value 19.0 units
	236	Thymol turbidity	11	4.6	Highest value 5.0 units
Infectious hepatitis	16	Gamma globulin	16	100.0	Lowest value 15.6 units
	16	Thymol turbidity	16	100.0	Lowest value 3.8 units
Hepatic cirrhosis	33	Gamma globulin	27	82.0	Lowest value 13.4 units
	32	Thymol turbidity	24	75.0	15 values below 5.0 units
Cholecystitis	33	Gamma globulin	3	9.1	Highest value 19.2 units
	33	Thymol turbidity	1	3.0	All values below 5.0 units
Obstructive jaundice: ma- lignant basis	12	Gamma globulin	2	17.0	Highest value 20.0 units
	12	Thymol turbidity	5	42.0	Highest value 6.0 units
Obstructive jaundice: be- nign basis	50	Gamma globulin	4	8.0	Highest value 24.0 units
	49	Thymol turbidity	11	22.5	5 values above 5.0 units

of positive values for gamma globulin turbidity than for thymol turbidity in alcoholic cirrhosis.

## COMMENT

Little is known of the mechanisms responsible for the production and maintenance of serum globulins.<sup>27, 28</sup> In their electrophoretic migration studies of serum globulin in hepatic disease, Gray and Barron<sup>1</sup> have observed elevations in the gamma globulin fraction, unaccompanied by recognizable alterations in total globulin, or in the albumin-globulin ratio. In the usual case of hepatic cirrhosis, decreases in albumin and elevations in total globulin are detectable by chemical means by the time such patients come to clinical study. Little

information is available on serum protein relationships early in the development of cirrhosis.

Studies in the formation of serum gamma globulins have borne particularly on the reticulo-endothelial system,<sup>10, 11, 29, 30</sup> the plasma cell<sup>31, 32</sup> and the lymphoid-lymphocyte system.<sup>33, 34</sup> White and Dougherty<sup>35, 36</sup> and Dougherty and associates<sup>37</sup> have concluded that adrenal cortical hormones of the 11-oxy type, under the activating influence of the anterior lobe of the pituitary, bring about the breakdown of lymphoid tissue and lymphocytes. Gamma globulin then may be released by alterations in lymphocyte cytoplasm. Murphy and Sturm<sup>38</sup> have demonstrated lymphoid hyperplasia with an enhanced potential for antibody formation in rabbits subjected to adrenalectomy.

On the other hand, the role ascribed to the adrenal cortex by Levin and Leatham<sup>39</sup> is that of aiding particularly in the maintenance of serum albumin. Maintenance of serum globulin is considered a function of the thyroid gland. Similarly, Hartman and co-workers<sup>40</sup> have found in adrenalectomized dogs and cats a fall in serum albumin, with some rise in serum globulin. McCullach and his co-workers<sup>41</sup> found normal values for serum gamma globulin in their electrophoretic studies of 4 patients with adrenal cortical failure of pituitary origin.

Although the available literature cannot be reconciled at present, further knowledge of the physiology of gamma globulin should be of tremendous value in furthering our understanding of the changes occurring in disease of the liver and biliary tract. There is some evidence<sup>42</sup> that in infectious hepatitis, the inflammatory changes may involve the reticulo-endothelial cells of the liver. Activation of these cells as a factor in the elevation of serum gamma globulin in infectious hepatitis is consistent with the reticulo-endothelial studies previously cited. The possible significance of this system in hepatic cirrhosis is not clarified at present.

Our studies indicate that the chief utility of the gamma globulin turbidity reaction is in the differential diagnosis of hepatobiliary disease. It is important in this connection to recall that elevations in serum gamma globulin may occur in a wide variety of conditions, usually associated with increased production of antibodies.<sup>1, 3, 11, 43, 44</sup> Such conditions must be borne in mind in the clinical application of gamma globulin studies.

Kunkel<sup>3</sup> has indicated that values for gamma globulin turbidity remain elevated late in the convalescent phase of infectious hepatitis, and hence is of clinical value in the evaluation of this period. Our limited experience to date is in support of this impression. In several of our cases of hepatic cirrhosis repeated studies have been made over periods of three months. Values for gamma globulin turbidity have remained consistently high during this period. The majority of these patients had well-advanced cirrhosis at the time of hospitalization. In 1 case, however, a value of 31 units was associated with

minimal symptoms, and evidence, at biopsy, of early, diffuse, minimal fibrosis. More information is needed concerning changes of gamma globulin in early cirrhosis.

In 6 of our 33 cases of hepatic cirrhosis turbidimetric values for gamma globulin were within our normal range (mean plus or minus two times the standard deviation). Two of these were considered alcoholic in etiology. In both of these cases, biopsy of the liver revealed good regeneration of hepatic cord cells. The third case was that of a girl 3 years old who later underwent splenectomy and a diagnosis of Banti syndrome was made. Plasma proteins in this case were 5.3 and 2.1 gm. per 100 cc. for albumin and globulin respectively. Trevorrow and associates<sup>24</sup> have indicated that an adult pattern of globulin is not established until the age of 5 years. The fourth patient gave a recent history of severe hematemesis and an old history of duodenal ulcer, with values of 2.8 and 1.7 gm. per 100 cc. for albumin and globulin respectively. The fifth patient was a man, 52 years old, whose chief complaint was repeated hemorrhage from esophageal varices. Results of other laboratory tests were within normal limits, and the clinical impression was that of old, stabilized or burned-out cirrhosis. In the sixth of these cases, laboratory procedures were associated with results within the normal ranges, and biopsy of the liver revealed good evidence of healing. Clinically, the disease in this case was considered to be compensated and the prognosis good. Certain of these findings are not consistent with the hypothesis of Kunkel and Hoagland<sup>4</sup> that elevated values for gamma globulin are associated with healing and regeneration of hepatic cells.

We believe the factors just mentioned should be considered in the evaluation of the results of the gamma globulin turbidity test in hepatic cirrhosis.

Our patients with cholecystitis and with obstructive jaundice who exhibited values for gamma globulin and thymol turbidity above the normal limits have usually presented a history of repeated obstruction or infection of the biliary tract over long periods and these frequently have been associated with repeated surgical procedures. In such cases, clinical suspicion of secondary cholangitis and biliary cirrhosis renders precise classification difficult at this time. In the absence of positive evidence of liver damage, we have placed these cases in their primary diagnostic grouping. This factor in tests of this type has been discussed by Althausen,<sup>45</sup> by Neefe and associates,<sup>12</sup> Mann and associates<sup>17</sup> and by Shay and Siplet.<sup>7</sup> High values from the thymol turbidity test have frequently been associated with high values for serum lipid in these cases, though this has not been an invariable finding.

We are summarizing in Table 5 the pertinent data on our patients, available to us from the laboratories of chemistry and of clinical pathology of the Mayo Clinic. More extensive comparisons have been made by Neefe and his asso-

ciates.<sup>12</sup> Data in Table 5 are not complete, but they afford a basis for our impression that the battery of available tests leaves much to be desired in the clinical study of hepatobiliary disease. The thymol turbidity reaction has been of considerable value in this regard. Our experience indicates that

TABLE 5  
*Summary of General Laboratory Data on Patient Groups Studied*

TEST MADE AND RESULT	CASES				
	Infectious hepatitis	Hepatic cirrhosis	Cholecystitis	Obstructive jaundice	
				Malignant	Benign
Sulfobromophthalein.....		15	12		
Retention > grade 2.....		8	2		
Cephalin-cholesterol flocculation.....	6	11	3	6	16
Flocculation > 2+.....	5	8	1	0	0
Prothrombin time.....	15	26	15	11	44
Elevated.....	9	19	7	2	3
Sedimentation rate.....	8	11	22	11	26
Elevated.....	7	2	14	10	25
Total cholesterol.....	9	16	9	10	22
Increased.....			1	7	
Decreased.....	6	3	2		3
Cholesterol esters.....	9	16	9	10	22
Increased.....			1		
Decreased.....	6	8	2	5	5
Serum globulin.....	10	21*		7	38†
> 3.0 gm. per 100 cc.....	8	18		0	5†

\* In 3 cases of cirrhosis in which the concentration of serum globulin was less than 3.0 gm. per 100 cc. the turbidimetric value for gamma globulin in the serum was normal.

† In 5 cases of obstructive jaundice in which the concentration of serum globulin was more than 3.0 gm. per 100 cc. the turbidimetric value for gamma globulin was normal.

accuracy in diagnosis may further be improved by the concurrent use of the gamma globulin turbidity estimation.

#### CONCLUSIONS

Studies of gamma globulin by a turbidimetric procedure on the blood serum of 236 donors to the blood bank have indicated a mean value of approximately 11 units, based on the turbidity of a standard suspension of barium sulfate as described. Tentatively, we have considered our upper limit of normal to be

approximately 16 units, which represents approximately our mean or average plus two times the standard deviation. Due to the variability of barium sulfate precipitation, it is suggested that individual normal ranges be established for each laboratory adopting this procedure.

Direct comparison between the gamma globulin turbidity and the thymol turbidity reactions have been made in cases of infectious hepatitis, hepatic cirrhosis, cholecystitis and obstructive jaundice. The value of the gamma globulin estimation as a diagnostic aid in these diseases has been discussed.

Serum lipid estimations by the turbidimetric procedure of Kunkel have shown considerable variation within these several groups. A tendency to high serum lipid values has been noted in obstructive jaundice. Results by this technic have averaged approximately 10 to 15 per cent higher than reports on the same serums from the laboratories of the Mayo Clinic in which chemical means of analysis were employed.

Gamma globulin estimations as described have indicated a low incidence of positive (high) values in normal subjects, and in patients with posthepatic disease of the biliary tract. A high incidence of elevated values has been found in infectious hepatitis and in hepatic cirrhosis. Additional advantages of the procedure are seen in the simplicity of the test and in the convenience, stability and reproducibility of the reagent buffer employed.

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## TURBIDIMETRIC ESTIMATION OF SERUM COLLOIDS IN EXTRAHEPATIC DISEASE

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In a previous communication, Snell and we have presented our studies of serum colloid changes in hepatobiliary disease, as measured by the turbidimetric procedures of Kunkel. The present paper extends these studies to patients whose diseases are not directly related to the liver or biliary tract.

On the basis of our findings in 236 blood bank donors, we have established our upper limits of normal for gamma globulin turbidity (16 units), for thymol turbidity (3.5 units), and for total serum lipids (880 mg. per 100 cc. of serum). An evaluation of normality should be carried out in each laboratory using these tests, because of possible variation inherent in the barium sulfate suspensions employed as turbidity standards.

Carter and MacLagan have reported a similar investigation of "liver function" tests in extrahepatic disease, based principally on the thymol turbidity and colloidal gold tests. These workers have found a high incidence of positive values in malaria, rheumatoid arthritis, congestive heart failure, glandular fever and subacute bacterial endocarditis. The higher degree of positivity noted with the colloidal gold reaction is ascribed to the narrower dependence of this test on gamma globulin. The data of these workers are in accord with the results obtained by Kunkel with the thymol turbidity reaction.

In agreement with Carter and MacLagan, we have found elevated values for gamma globulin and for thymol turbidity in several disease entities not directly related to the hepatobiliary system. It has not been shown that these reactions are specifically indicative of liver damage. Elevated values may reflect liver damage secondary to systemic toxemia, increased antibody production or variable combinations of these possibly with other factors as yet unknown.

We cannot as yet describe the basic mechanisms underlying these serum colloid changes. The clinical interpretation of these tests should nevertheless consider those conditions other than hepatobiliary disease in which elevated values may be expected. With caution, the tests may be of aid in the evaluation of liver changes secondary to those conditions.

### METHODS

Values for gamma globulin turbidity, for thymol turbidity and for total serum lipids were determined as previously described. Serum samples were analyzed within twenty-four hours of withdrawal, to avoid the irregular changes we have noted in samples repeatedly studied during two to fifteen days.



Diagnostic classifications have been established by clinical criteria, supported when possible by the results of surgical, pathologic or laboratory examination.

#### MATERIAL AND RESULTS

We have previously described a "miscellaneous hospital population," consisting of 114 hospitalized patients, whose illnesses were considered unrelated to specific alterations in serum colloids. We were able to show that turbidity values for gamma globulin were significantly lower and more variable in this group than in our donor control groups. A broad classification of the members of this miscellaneous group is presented in Table 1. This table includes subjects studied since our previous report.

Similar studies have been carried out on serum samples from 233 additional hospital patients classifiable into more discrete diagnostic groups. Our data on these patients are summarized in Table 2.

#### COMMENT

It is evident from Table 2 that the findings of elevated gamma globulin turbidity and thymol turbidity are not peculiar to cases of primary liver disease. We cannot at present exclude secondary liver damage as a factor in these disturbances of serum colloids.

Low values for gamma globulin have been found in a number of conditions associated clinically with nutritional disturbance. These are noted particularly in peptic ulcer, in gastro-intestinal malignant lesions, in many cases of ulcerative colitis and in the nephrotic syndrome. Conditions of malnutrition have been implicated by others in the production of secondary liver damage with elevated thymol turbidity values. Krebs has described depression of total globulin and of gamma globulin in a malnourished patient. Clinical and serum protein improvement followed dietary correction.

The significance of these changes to the patient is not clear. In view of the complex nature of the thymol turbidity reaction, it is reasonable to assume that elevations in gamma globulin are more nearly related to increased antibody protein. Carter and MacLagan similarly have expressed the belief that the thymol turbidity test is more closely related to liver damage than to antibody globulin per se. Clarification of the fundamental processes involved should lend to these tests prognostic as well as diagnostic values.

Eaton and associates have discussed the literature indicating an antigenic role for products of tissue damage. Antigenic products of diseased liver tissue are suggested as responsible for the production of the heterogenetic antibody which these workers have found in many cases of infectious hepatitis.

Reticulo-endothelial and related cells have been frequently implicated in the formation of serum gamma globulin. These considerations favor the hypothe-

TABLE 1

*General Classification of Patients in Miscellaneous Hospital Population, with Data on Turbidimetric Estimations of Serum Samples*

CLINICAL CATEGORY	DETERMINATION	CASES	MEAN VALUE	RANGE	VALUES OUTSIDE NORMAL RANGE
Psychiatric	Gamma globulin	3	9.3 units	7.0-10.4	0
	Thymol turbidity	3	1.7 units	1.5- 1.8	0
	Total lipids	3	627 mg.*	480-720	0
Neurologic	Gamma globulin	20	9.8 units	5.6-18.0	1
	Thymol turbidity	18	1.9 units	0.8- 3.0	0
	Total lipids	8	648 mg.*	465-875	0
Cardiovascular	Gamma globulin	18	11.1 units	5.4-25.0	2
	Thymol turbidity	17	1.9 units	1.0- 4.2	2
	Total lipids	13	675 mg.*	430-875	0
Hematologic	Gamma globulin	15	10.7 units	4.2-17.0	1
	Thymol turbidity	14	1.8 units	0.8- 3.3	0
	Total lipids	11	564 mg.*	360-675	0
Renal (other than nephrosis or nephritis)	Gamma globulin	6	10.0 units	8.4-12.0	0
	Thymol turbidity	6	2.0 units	1.4- 3.5	0
	Total lipids	6	584 mg.*	425-755	0
Gastro-intestinal (other than ulcer or malignant lesions)	Gamma globulin	29	9.2 units	3.2-18.0	1
	Thymol turbidity	26	1.9 units	0.8- 4.8	2
	Total lipids	16	626 mg.*	470-885	1
Gynecologic	Gamma globulin	9	9.4 units	4.6-19.2	1
	Thymol turbidity	9	2.0 units	0.6- 4.5	1
	Total lipids	7	638 mg.*	500-720	1
Orthopedic	Gamma globulin	4	9.9 units	8.6-12.0	0
	Thymol turbidity	4	2.0 units	1.0- 2.6	0
	Total lipids	1	600 mg.*		
Neoplastic (other than gastro-intestinal)	Gamma globulin	7	8.9 units	5.6-14.0	0
	Thymol turbidity	7	1.7 units	1.2- 3.0	0
	Total lipids	5	596 mg.*	545-655	0
Localized abscesses	Gamma globulin	9	12.2 units	7.0-21.6	1
	Thymol turbidity	9	2.4 units	1.5- 3.5	0
	Total lipids	6	603 mg.*	480-825	0
Diabetes mellitus	Gamma globulin	3	14.3 units	6.4-28.4	1†
	Thymol turbidity	3	2.7 units	1.0- 4.5	1†
	Total lipids	3	793 mg.*	560-1,250	1
Sprue syndrome	Gamma globulin	3	10.6 units	8.4-13.6	0
	Thymol turbidity	1	5.2 units		
	Total lipids	2	490 mg.*	450-525	0

\* Per 100 cc. of serum.

† Diabetes in this case was complicated by stasis ulcer, and by coexisting hay fever and bronchial asthma.

TABLE 2

*Turbidimetric Estimations of Serum Colloids in 232 Patients with Extrahepatic Disease*

DIAGNOSTIC CLASSIFICATION	DETERMINATION	CASES	MEAN VALUE	RANGE	REMARKS
Peptic ulcer	Gamma globulin	66	8.9 units	5.0-20.0	Values > 16 = 1
	Thymol turbidity	64	1.7 units	0.7- 4.6	Values > 3.5 = 2
	Total lipids	40	664 mg.*	465-1,070	
Gastro-intestinal malignant lesions	Gamma globulin	67	10.2 units	4.0-28.0	Values > 16 = 8
	Thymol turbidity	66	2.0 units	0.5- 6.6	Values > 3.5 = 4
	Total lipids	45	608 mg.*	420-1,040	
Chronic pancreatitis	Gamma globulin	12	11.3 units	5.6-17.2	Values > 16 = 2
	Thymol turbidity	12	2.1 units	0.8- 4.0	Values > 3.5 = 1
	Total lipids	10	731 mg.*	460-935	
Rheumatoid arthritis	Gamma globulin	21	23.5 units	9.2-84.4	Values > 16 = 16
	Thymol turbidity	21	4.4 units	1.8-11.5	Values > 3.5 = 7
	Total lipids	16	644 mg.*	480-875	
Gouty arthritis	Gamma globulin	12	13.2 units	7.8-26.4	Values > 16 = 1
	Thymol turbidity	10	2.9 units	1.5- 4.4	Values > 3.5 = 3
	Total lipids	8	767 mg.*	520-975	
Acute glomerulonephritis	Gamma globulin	7	17.8 units	8.5-27.6	Values > 16 = 4
	Thymol turbidity	6	3.3 units	2.0- 5.2	Values > 3.5 = 2
	Total lipids	3	575 mg.*	435-765	
Nephrosis	Gamma globulin	7	5.4 units	1.3-12.0	Values > 16 = 0
	Thymol turbidity	7	10.0 units	4.0-22.2	Values > 3.5 = 7
	Total lipids	4		1,700- >2,500 mg.*	
Chronic ulcerative colitis	Gamma globulin	30	14.0 units	5.0-49.0	Values > 16 = 9
	Thymol turbidity	28	3.3 units	1.2- 7.5	Values > 3.5 = 7
	Total lipids	16	549 mg.*	330-770	
Multiple myelomas	Gamma globulin	4	24.6 units	0.4-61.0	Values > 16 = 2
	Thymol turbidity	4	1.7 units	0.3- 5.0	Values > 3.5 = 1
	Total lipids	4	570 mg.*	385-785	
Disseminated lupus erythematosus	Gamma globulin	5	44.5 units	19.0-79.0	Values > 16 = 5
	Thymol turbidity	5	8.2 units	3.5-10.5	Values > 3.5 = 4
	Total lipids	5	583 mg.*	420-835	
Infectious mononucleosis	Gamma globulin	3	23.4 units	20.4-25.0	Values > 16 = 3
	Thymol turbidity	3	6.0 units	4.5- 7.2	Values > 3.5 = 3
	Total lipids	2	610 mg.*	600-620	

\* Per 100 cc. of serum.

sis that gamma globulin alterations may reflect the individual response to some type of specific stimulus. An evaluation of this response may in turn aid in the clinical evaluation of the patient. Consistent with this view is the reported efficacy of human gamma globulin in the prophylaxis of infectious hepatitis. Effective antibodies for such use have been found in the Cohn fraction II of pooled human plasma.

We have not observed any constant correlation between the degree of elevation of turbidity values and the severity of the associated disease process. There is undoubtedly a lag phase in the development of an antibody response to a specific stimulus if present. It is interesting to speculate that an inadequate response may have been a factor in cases of acute fulminating infectious hepatitis associated with only moderate elevations in serum turbidity values. Several such cases have been noted in our previous series.

#### *Peptic Ulcer, Gastro-intestinal Malignant Lesions, Pancreatitis*

These categories became of interest to us because of their possible inclusion with hepatobiliary disease in the differential diagnosis of symptoms referable to the abdomen.

In our group of 66 patients who had peptic ulcer, a marked tendency to low gamma globulin values was noted. The majority of these lie within the range of 5 to 9 units. In the one patient whose value exceeded normal limits, the ulcer history in a 56 year old woman was complicated by evidence of renal inadequacy, and a questionable history of venereal lymphogranuloma with rectal stricture. Serum proteins were 4.0 gm. of albumin and 3.5 gm. of globulin per 100 cc.\* Elevation of serum gamma globulin in venereal lymphogranuloma has been reported by Gutman and co-workers.

A similar tendency to low gamma globulin turbidity is seen in the majority of our 67 cases of gastro-intestinal malignant lesions. In 8 of the cases elevated gamma globulin values were found, while thymol turbidity was elevated in 4 cases. These patients exhibited advanced malignant lesions, with widespread abdominal carcinomatosis or hepatic involvement or both.

In 2 of our 12 cases of chronic pancreatitis, gamma globulin values were slightly above our upper limit of normal (17.2 and 16.4 units). In one of these, a slight elevation (4 units) was noted in thymol turbidity. Normal values were found in the remaining 10 cases, and we do not attach any significance to the slight elevations observed in the 2 cases. Normal values were found in 1 case of acute pancreatitis. Low values (6.0 and 7.6 units) for gamma globulin were obtained in 2 cases of surgical diabetes due to complete pancreatectomy.

Elevation of gamma globulin in patients having malignant disease might be

\* Henceforth in this paper, the form "4.0/3.5 gm. per 100 cc." will be used.

expected, in conformity with the hypothesis of Eaton and associates ascribing antigenic activity to products of tissue destruction. This has not been our experience, in the absence of hepatic involvement. The possibility of a fundamental difference between tissue damage due to benign and to malignant causes cannot be excluded.

### *Arthritis*

Carter and MacLagan reported positive colloidal gold reactions in 76 per cent of 34 cases of rheumatoid arthritis. Thirty-eight per cent of these patients manifested elevations in thymol turbidity. Increased turbidity values in these patients were believed to be due to increased antibody production, with the greater incidence of positivity in the colloidal gold reaction related to the greater specificity of this test for gamma globulin. Only occasional elevations were noted in other types of arthritis.

The agreement of our data with those of Carter and MacLagan is seen in Table 2. In 16 of our 21 cases of rheumatoid arthritis gamma globulin values were found to be elevated, while thymol turbidity was increased in only 7 of these cases. Gamma globulin turbidity was within normal limits in 11 of 12 cases of gouty arthritis.

Our results argue against the use of these tests in the evaluation of liver function prior to gold therapy for rheumatoid arthritis. They indicate a fundamental difference between rheumatoid arthritis and other types of arthritis, which is reflected in the serum proteins.

### *Nephritis and Nephrosis*

Elevated values for gamma globulin were obtained in 4 of 7 cases of acute glomerulonephritis. In 2 of these, thymol turbidity values were increased. Normal turbidity values were found in 2 cases of subacute, and 2 cases of chronic glomerulonephritis.

Each of 7 patients who had nephrosis exhibited low values for gamma globulin. In 3 of these cases, total globulin exceeded the value of 3 gm. per 100 cc. considered to be the upper limit of normal. Thymol turbidity exceeded the normal in each of these 7 patients. These increases in thymol turbidity may be due in part to the elevated total lipids noted in these patients. There is no evidence that these elevated values indicate hepatic damage in nephrosis.

The electrophoretic studies of Longsworth and MacInnes indicate that globulin elevation in nephrosis is due to increased beta globulin fractions. Kagan reported normal values for total globulin by chemical methods in 78 of 79 cases of nephrosis. Globulin values of more than 3 gm. per 100 cc. were obtained in 50 per cent of 40 cases of acute glomerulonephritis. Increased antibody pro-

duction may be a factor in the hyperglobulinemia and hypergammaglobulinemia of acute glomerulonephritis.

### *Chronic Ulcerative Colitis*

Tumen and co-workers described 5 cases of advanced liver disease in a series of 151 cases of chronic ulcerative colitis. Similar findings by Comfort and associates, and by Cain and Callen, were discussed. Ross and Swarts described cirrhotic changes in the livers of 2 patients studied, and further found evidences of liver damage in 14 of 27 cases in which autopsy was performed. Thirty-five of 100 general autopsies revealed equivalent evidence of liver damage in the opinion of these workers. Liver damage, when present, is ascribed to factors of toxemia, chronic disease, protein loss per rectum and other nutritional deficiencies.

Elevated gamma globulin values were observed in 9 of the 30 cases in our series. In 7 of these, thymol turbidity exceeded 3.5 units. These elevations did not show any significant correlation with the duration or severity of the disease, or with the plasma protein levels.

Of the remaining cases in our series, 7 were found to have values of less than 8 units of gamma globulin turbidity. Malnutrition may play a role in these low values, as indicated by Krebs.

Although not specific for liver damage, these tests may through more frequent use become of value in the recognition of concomitant hepatitis in chronic ulcerative colitis. Tumen and associates have expressed a similar view.

### *Multiple Myelomas*

The literature is indicative of wide variations in serum protein patterns in this condition. In the electrophoretic studies of Longsworth, Shedlovsky and MacInnes, 2 patients were found to have markedly elevated beta globulin, with low normal values for gamma globulin. Normal serum protein values were obtained in their third case. Kekwick obtained elevated globulin values, proportional to the increases in total protein, in each of 5 cases. In 4 of these, the increased globulin was due to the gamma fraction, while the fifth was found to have low gamma globulin with high values for the beta globulin fraction. Further studies by Gutman and associates and by Moore and others confirm the classification of multiple myeloma patients into three groups based on protein patterns: (1) those having hyperglobulinemia due to the gamma fraction; (2) serums with or without hyperglobulinemia in a variety of patterns including excesses of beta globulin, of Bence Jones protein or of unusual components designated as "M"; (3) serums with essentially normal protein patterns. Kekwick expressed the belief that elevated gamma globulin may be due to antibody formation, to Bence Jones protein, or to pathologic changes at the site of for-

mation of gamma globulin. Others have implicated the plasma cell in the formation of this protein.

Each of our 4 cases of multiple myelomas was confirmed by roentgenologic studies and by sternal marrow aspiration. In 2 of these, extremely low values for gamma globulin were found (0.4 and 3.0 units). In the first of these, serum albumin was 3.1, serum globulin was 6.2 gm. per 100 cc. and Bence Jones proteinuria was not demonstrable. Urine in the second case was positive for Bence Jones protein, and serum proteins were 4.3/1.4 gm. per 100 cc.

Gamma globulin values were elevated in our third and fourth cases (34 and 61 units). Hyperglobulinemia and Bence Jones proteinuria were manifest in the first of these 2 cases.

The significance of these differences is not understood. They are in conformity with the variations in protein patterns noted in the literature on multiple myelomas.

### *Disseminated Lupus Erythematosus*

Coburn and Moore found reversal of the albumin-globulin ratio, associated with lowered albumin, elevated globulin and essentially normal total protein, in the serums of 17 cases of disseminated lupus erythematosus. In 6 of these cases, liver sections revealed fatty degeneration and focal necrosis.

Serum gamma globulin turbidity was elevated in each of our 5 cases. Some elevation of thymol turbidity was noted in 4 of these; serum lipids were not abnormal. We have obtained normal turbidity values in 1 case of discoid lupus erythematosus, and in 1 case of erythema nodosum. Mulvehill found no constant alteration of serum proteins in the common dermatoses.

### *Infectious Mononucleosis*

Cohn and Lidman have commented on the similarity in clinical picture between infectious mononucleosis and infectious hepatitis. They reported a high incidence of positive thymol turbidity values in nonicteric cases of infectious mononucleosis, and considered this to be evidence for concomitant hepatitis. Six cases studied electrophoretically revealed a "picture of early hepatitis": slightly decreased serum albumin, some elevation of alpha and beta globulins and rather marked elevation of gamma globulin. Control patterns of uncomplicated cases of infectious mononucleosis were not described.

In the 19 cases studied by Carter and MacLagan, colloidal gold flocculation was positive in 95 per cent and thymol turbidity was elevated in 58 per cent. They ascribed these alterations to antibody formation and to liver damage in varying degree. Ziegler demonstrated hepatitis in the sections prepared from the liver in a case of mononucleosis and expressed the belief that jaundice in the latter condition is due to associated hepatitis. Evans found cephalin-cholesterol flocculation of 2+ or more in 95 per cent of 19 nonicteric cases of infec-

tious mononucleosis, and considered these results to be indicative of associated hepatitis.

Gamma globulin values have been elevated in each of our 3 cases of infectious mononucleosis, together with some elevation of thymol turbidity in each. In 1 of these cases, a diagnosis of associated hepatitis was made, on the basis of an elevated serum bilirubin and clinical jaundice. In view of the association of antibody with gamma globulin, and of the nonspecific nature of the thymol turbidity reaction, it is difficult to justify the assumption of hepatitis in these cases in the absence of jaundice. The use of these turbidity reactions in the differential diagnosis of infectious mononucleosis and infectious hepatitis should imply careful consideration of this fundamental question.

### *Miscellaneous*

An isolated case of considerable interest was that of a  $3\frac{1}{2}$  year old boy who entered the hospital for skin grafting to an area severely burned some few weeks prior to entry. Serum obtained five days after admission exhibited 25 units of gamma globulin turbidity and 4 units of thymol turbidity. Serum proteins were 3.7/3.9 gm. per 100 cc. On the fourteenth day in the hospital, gamma globulin turbidity had risen to 50 units, thymol turbidity to 7.3 units and the serum proteins were 2.9/4.5 gm. per 100 cc. Prothrombin time was 22 seconds (normal range 17 to 19), and the cephalin-cholesterol flocculation was 4+. Ten days later, on the twenty-fifth day in the hospital, cephalin-cholesterol flocculation was negative. Serum studied seven weeks after entry revealed gamma globulin turbidity of 34 units and thymol turbidity of 6 units. Hemoconcentration was not demonstrable in any of these periods and the cause for these changes in turbidity values is not known. The possibility of liver damage secondary to the severe burn, or of antibody formation in response to damaged skin or other tissues, cannot be excluded.

### CONCLUSIONS

1. Turbidimetric estimations of serum gamma globulin, thymol turbidity and total lipids have been described in diseases not directly related to the hepatobiliary system.
2. Low values for gamma globulin are the rule in peptic ulcer, gastro-intestinal malignant lesions and pancreatitis. Malnutrition is suggested as a factor in this finding. Gamma globulin values were uniformly low in 7 patients who had nephrosis.
3. A high incidence of elevated gamma globulin is noted in rheumatoid arthritis, acute glomerulonephritis, disseminated lupus erythematosus and infectious mononucleosis. This may be related to antibody formation, to associated liver involvement or to combinations of these and other factors.
4. Nine of 30 cases of chronic ulcerative colitis were found to have elevated



gamma globulin. Thymol turbidity was increased in 7 of these. Further study may verify the utility of these tests in the recognition of hepatitis associated with chronic ulcerative colitis.

5. Our series of 4 patients with multiple myelomas includes 2 cases of elevated gamma globulin and 2 cases in which these values were very low. These results do not parallel the serum protein values for these patients as determined by chemical means.

6. Use of the turbidimetric procedures in the differential diagnosis of hepatobiliary disease should consider entities, not directly related to the liver, in which elevated values may be expected. Mechanisms underlying changes in turbidity, and the significance of these to the patients, are not adequately explained.

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## ANALYSIS OF 1500 "ROUTINE" PROCTOSIGMOIDOSCOPIC EXAMINATIONS

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### INTRODUCTION

The value of proctosigmoidoscopic examination in the diagnosis of the cause of rectal symptoms is generally recognized. The standard textbooks on proctology, gastroenterology, internal medicine and surgery are unanimous in recommending this procedure. Bockus<sup>1</sup> states, "It (proctosigmoidoscopy) is required in the investigation of cases of constipation, diarrhea, bleeding from the bowel, abdominal discomfort related to bowel function or obscure abdominal symptoms suggesting organic disease unexplained by other routine studies."

That the procedure is simple, consumes little time, and is easily learned is also conceded, yet it is frequently ignored as witnessed by the patients who have complained of "piles" and have been given suppositories or ointment for treatment without even a digital rectal examination, or who sometimes have even been subjected to surgery for hemorrhoids, when carcinoma, ulcerative colitis or similar serious disease is present.

The purpose of this study is to determine the value of "routine" proctosigmoidoscopic examinations. Recently wide-spread interest in detection of early cancer has arisen; many cancer detection clinics have been formed, and many roentgen-ray examinations of the stomach and colon are being done in hospitals and clinics in the attempt to detect cancer at an early period when it is amenable to treatment. The question arises as to whether or not a simple procedure, such as proctosigmoidoscopic examination, done routinely in patients 30 years of age and over, might be of value in the recognition of early rectal carcinoma. Again we quote from Bockus:<sup>2</sup> "Sixty to 75 per cent of all colonic carcinomas are within reach of a 10-inch sigmoidoscope. . . . The examination is life-saving in many instances because of early discovery of a lesion not shown roentgenologically. Early carcinoma may be found accidentally by sigmoidoscopy during the course of a routine diagnostic survey."

### METHOD

1500 patients were proctoscoped either as part of a routine general physical checkup or as part of a gastrointestinal survey. None of the patients who had any complaint whatsoever of diarrhea, rectal bleeding, rectal or anal pain, pruritis, hemorrhoids or of recent abnormality or change in bowel habits was included in this group.

In the course of obtaining the 1500 routine examinations, 393 other patients who did have some rectal complaints were proctoscoped. The rectal complaints in this group frequently were minor, and the examination was often done as part of a routine diagnostic survey. However, because they did have a rectal complaint, the results are listed separately.

#### ANALYSIS OF 1500 ROUTINE PROCTOSIGMOIDOSCOPIC EXAMINATIONS

Table I lists the findings in this group of 1500 examinations. Five of the patients were found to have carcinoma; 79 had polyps which were removed and found to be benign. Three patients had chronic ulcerative colitis; 40 had rectal ulcers, pinpoint in type, which the examiner felt probably represented an early, low-grade ulcerative proctitis. Amebiasis was suspected at two examinations,

TABLE I  
*Findings on 1500 Consecutive Routine Proctosigmoidoscopic Examinations*

	NO. CASES
Rectal carcinoma.....	5
Benign polyps.....	79
Ulcerative colitis.....	3
Nodular prostate.....	7
Prostatic cancer.....	3
Pinpoint rectal ulcers.....	40
Anal fissure.....	22
Submucous fibroma.....	2
Stricture.....	3
Extra-rectal mass.....	1
Amebic ulcers.....	2

and an extrarectal mass was felt in one; this had not been noted on routine digital examination. Nodular prostate was noted on digital examination in seven cases, and in three others proven cancer of the prostate was first suspected at the time of the digital rectal examination done in conjunction with the endoscopy. Cases in which lesions were found by means of digital rectal examination as part of the routine physical examination were excluded from these figures. Thus, although these figures individually are statistically small, the total number of these various significant lesions forms 9.3 per cent of the total cases when compared with the entire group.

#### CASE REPORTS: CARCINOMA OF THE RECTUM

*Case 1.* A 39 year old white female complained of distention, life-long constipation and lower abdominal cramps. Clinically her complaints were those of irritable colon. Routine proctoscopic examination revealed a fungating, ulcerated cauliflower

growth that bled readily; it was not of sufficient size to have caused symptoms. Biopsy revealed an adenocarcinoma, Grade I. The patient had surgery elsewhere.

*Case 2.* A 59 year old white male was seen because of nervousness and weakness. The only gastrointestinal complaint was that of occasional "gas." Barium enema and stomach x-rays were negative. Routine proctoscopic examination revealed a large rectal polyp that was ulcerated and bleeding, lying  $5\frac{1}{2}$  inches above the anal sphincter. Biopsy tissue removed on 2-7-47 revealed a benign rectal polyp; biopsy tissue excised 2-13-47 revealed a Grade II adenocarcinoma with hyperchromatic cells, numerous mitotic figures, atypical glands.

*Case 3.* A 55 year old white male came to the hospital because of heartburn relieved by soda. Routine proctoscopic examination revealed a sessile, pea-sized, red, non-ulcerated polyp at six inches. This was removed and reported histologically benign. However, within a month a large, recurrent, non-ulcerated polyp was found, removed, and pronounced to be an adenocarcinoma, Grade II, with anaplastic cells and invasion of the rectal mucosa. More of the mucosa was removed from this site two weeks later and was entirely normal. Repeated progress examination up to one year after removal have been negative for recurrence.

*Case 4.* This 50 year old white male was seen because of epigastric distress. He had no colon or rectal symptoms. Routine examination revealed a small polyp on the anterior surface of the rectum  $3\frac{1}{2}$  inches up. Removal of this polyp revealed it to be adenocarcinoma, Grade I, with hyperchromatic nuclei, loss of polarity, and frequent mitotic figures. The basement membrane was broken through. Repeated proctoscopic examinations for two years have failed to reveal any recurrence.

*Case 5.* A white male, age 66, complained of "stomach trouble" with belching one-half hour after meals and with relief from alkalis. Proctoscopic examination showed a carcinoma at five inches with two large, friable, bleeding polyps. Biopsy on 10-1-47 and 10-6-47 showed benign findings. Because of the size of the polyps and their gross appearance it was felt that resection was indicated, and on 10-18-47, an anterior resection of the polyp-bearing area was done. Histologically, sections through the large, raised, papillomatous lesions showed "some areas near the tip where the epithelium becomes anaplastic and there is piling up of the tall cylindrical cells. Sections of the bowel on either side of the polyps show no abnormality." Adenocarcinoma, Grade I.

#### COMMENT

We believe the finding of 5 carcinomas and 79 rectal polyps, all of which would have gone undetected if a routine proctoscopic examination had not been done, is extremely worthwhile. Admittedly, it requires time and patience to do 1500 routine proctoscopic examinations; however, when the time required

for one of these examinations is estimated to average 5 minutes, then the 125 hours required to diagnose 5 early rectal carcinomas seems little when compared with the added length of life of these patients.

We would point out, in addition, that these lesions were detected early enough so that extensive surgery was not necessary. Simple removal of the carcinoma and fulguration in early cases will frequently suffice. In none of these cases was abdominal perineal resection with permanent colostomy necessary. Furthermore, other rectal lesions were found. Seventy-nine other patients had benign rectal polyps. While there is difference of opinion as to whether or not these may become malignant<sup>3</sup>, the consensus is that it is much safer to remove them.

TABLE II

*Findings on 393 Consecutive Proctosigmoidoscopic Examinations upon Patients with Rectal Symptoms*

FINDINGS	SYMPTOMS				
	Rectal bleeding	Diarrhea	Pain	Pruritis	"Hemorrhoids"
Rectal carcinoma.....	3	3	0	0	0
Rectal polyps.....	11	6	0	0	2
Ulcerative colitis.....	7	15	0	0	0
Fistula.....	0	0	1	0	0
Rectal stricture.....	0	0	0	0	1
Amebic ulcers.....	1	3	0	0	0
Tuberculous ulcers.....	0	1	0	0	0
X-ray proctitis.....	1	0	0	0	0
Lymphogranuloma venereum.....	1	0	0	0	0

#### ANALYSIS OF 393 EXAMINATIONS DONE ON PATIENTS WITH RECTAL COMPLAINTS

The results of these examinations are found in Table II. As might be suspected, the percentage of patients revealing significant disease was considerably higher in the group with symptoms referable to the rectum. Of the entire group, 20 per cent had major disease, such as carcinoma, ulcerative colitis, etc. Nineteen and one-half per cent of those with rectal bleeding and 22 per cent with complaints of diarrhea had such major disease.

Of the group of six cancers of the rectum found in this series as a result of proctosigmoidoscopic examination done because of symptoms pointing to a probable rectal lesion, three had diarrhea and three had bleeding as a complaint. The following two cases are presented as typical of this group:

*Case 1.* A white female, age 58, complained during the course of treatment for arthritis of four recent episodes of slight rectal bleeding. She was referred to this

clinic and a carcinoma found. It extended from the four-inch level to six inches, involving three-fourths of the circumference of the bowel. Biopsy revealed a Grade II adenocarcinoma which microscopically was "covered in part by normal glandular epithelium, but beneath the surface and beneath the muscularis mucosae are cellular epithelial masses with formation of numerous intra-epithelial acinar structures and some papillary areas. The epithelium is moderately pleomorphic with abundant pink-staining cytoplasm, and where acini are formed it is columnar in type. Nuclei are chromatic and there are many mitoses." The patient was operated on 5-20-47 and a first-stage abdominal perineal resection done. She subsequently died of pulmonary embolus before the surgery could be completed.

*Case 2.* A 52 year old white male complained of moderate constipation of 10 years duration. About three months before admission he had started the use of mineral water laxative with diarrhea resulting. This could not be controlled, in spite of the efforts of his local physician.

Earlier, on the day of his admission to Henry Ford Hospital, he had received an enema which resulted in passage of blood, and he was referred for diagnosis. Proctoscopic examination revealed a firm, polypoid, bleeding mass, four inches up in the rectum. The patient was advised to have resection and returned to his local physician.

#### COMMENT

In neither of these cases had symptoms been present for a long time; however, in neither was there a lesion which could be removed with the biopsy forceps and followed by frequent proctosigmoidoscopic examinations as was true in cases 3 and 4 of the routine group. This was true of the entire latter group of six patients with carcinoma of the rectum.

#### SUMMARY

A review of 1500 consecutive proctosigmoidoscopic examinations showed that these examinations done routinely, as part of general diagnostic studies, will reveal a significant number of rectal diseases. Five cases of rectal cancer, four of which occurred in rectal polyps, and 79 benign polyps were detected by routine examination. The examinations were conducted without any untoward incident, demonstrating the relative safeness of the procedure. The number of rectal cancers detected by routine examination constituted nearly half of those found in the entire series, although the percentage of similar conditions found in the group with definite rectal symptoms was much tigher.

#### CONCLUSIONS

1. Routine proctosigmoidoscopic examinations will frequently reveal serious rectal disease which would not be suspected from history or physical findings, including digital rectal examination.

2. The lesions so found will often be more amenable to treatment than when they are allowed to progress to a stage where they cause symptoms.

3. Proctosigmoidoscopy is a simple, safe procedure when properly done. It consumes little time.

4. Proctosigmoidoscopic examination may well be made a part of every complete diagnostic study, whether or not gastrointestinal symptoms are present.

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## ALTERATIONS IN COLONIC FUNCTION IN MAN UNDER STRESS

### II. EXPERIMENTAL PRODUCTION OF SIGMOID SPASM IN HEALTHY PERSONS\*

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#### INTRODUCTION

Previous studies<sup>1</sup> from this laboratory have shown that healthy persons often exhibit spasm and mucosal engorgement in the sigmoid colon when they are under stress induced by painful experimental procedures. These observations were made upon only a small number of subjects; the method of recording was subject to errors in interpretation; and the stimuli were limited in variety, being physically painful experiences quite unlike the life situations confronting the average patient with "irritable colon." For these reasons further studies have been made upon the function of the sigmoid colon in healthy persons under stress, utilizing either direct proctoscopic observation or a balloon technique.

#### METHODS

The subjects of these experiments were medical student volunteers and patients with no clinical evidence of disease or dysfunction of the colon. The patients had been hospitalized for a variety of diseases, but were ambulatory and in good general condition at the time of the observations here recorded. All subjects were prepared for the experiments by enemas of physiological saline until clear, and by omission of food for six hours or more.

In some instances continuous proctoscopic observations of the lower sigmoid colon were made and recorded in the manner previously described.<sup>1</sup>

In the remaining experiments, the contractile state of the sigmoid colon was continuously recorded by the kymographic method. A distensible latex balloon 10 cm. in length was inserted through the proctoscope to a point 20 to 40 cm. from the anus. It was then inflated with air and connected through a flexible rubber tube to a water manometer. Descent of the balloon from its original position was rare, and when it occurred the experiment was excluded from consideration. In many instances, gastric motility was simultaneously recorded by a similar balloon passed orally. This provided a check upon changes in intra-abdominal pressure as possible causes of variations in the sigmoid tracing. The details of this method of recording, together with the variations in resting motility patterns in healthy persons, will be reported separately.

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The stimuli have included cold pain, compression of the head, induced hypoglycemia, and the discussion of real or imagined situations which might be disturbing to the individual. These stimuli were intended to produce stress in our subjects—we expected that they would regard these experimental situations as threats to their security.

Much importance attaches to the manner in which it was concluded that stress had been produced in a given experiment. No single feature could be used as a sole criterion of stress; the decision rested upon observation of the subject's general behavior and his report of his emotional reactions. Many subjects would moan, make restless movements, and use highly colored language to describe their suffering. We would observe physical signs such as

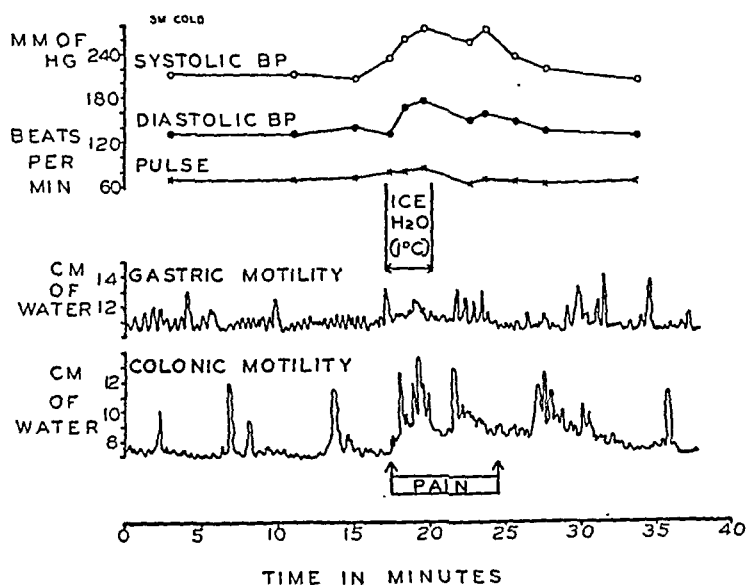


FIG. 1. Pressor response and augmentation of colonic motility associated with cold pain.

sighing, sweating, pallor, or elevated blood pressure. In discussing the experiment later, the subject often revealed that he had been profoundly disturbed and had developed an emotional conflict. If many of these criteria had been fulfilled, we concluded that stress had been produced.

## RESULTS

### Cold Pain

In 22 experiments on 17 subjects, intense pain was produced by submerging the right hand for five minutes or more into ice water at a temperature of 0–1°C.

This experiment was performed on a hypertensive subject (Fig. 1), who reported severe pain and developed a distinct cold pressor response. The colonic

contractions were greatly increased, and this augmentation outlasted both the period of immersion of the fingers and the period of perception of pain.

✓ In another subject, the colonic response to this form of stress was observed proctoscopically (Fig. 2). Soon after immersion of his hand, he reported pain, and described it as severe. ✓ He remained calm for the first eight minutes, but then suddenly became agitated and resentful, cried "This is torture," and despite our objections removed his hand from the water, with rapid disappearance of the pain. > Coincident with his outburst of temper, occlusive spasm and moderate engorgement were observed in the colon.) These changes slowly subsided as the subject regained his composure. Both the colonic changes and the emotional outburst began much later and ended much later than the pain itself.

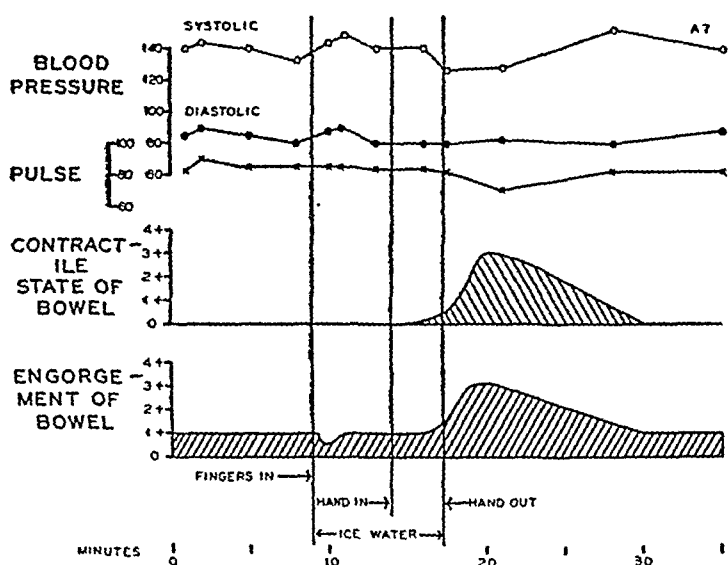


Fig. 2. Colonic changes accompanying an emotional reaction to the experience of cold pain (see text).

In all 22 experiments, pain of high intensity was produced. In thirteen experiments, the contractile state of the sigmoid colon was significantly increased. In all of these thirteen observations it was judged, from the criteria previously mentioned, that stress had been produced. In the remaining observations the subjects did not appear under stress, and no colonic changes were obtained. Five subjects underwent this experiment twice, with an interval of 30 minutes to four weeks. In one of these subjects, the colonic response was obtained on both occasions; in two it was never obtained. In the remaining two the bowel reacted on the former occasion but not on the latter; it was evident from both the statements and the behavior of these subjects that the first experience with cold pain had been regarded with apprehension, and that the second had not.

## Headscrew

Four subjects endured a severe headache produced by compressing the head with a metal band containing rubber-cushioned screws. The screws were tightened by the subjects themselves. The headache was maintained at a high level of intensity for twenty to thirty minutes, then terminated abruptly by the removal of the "headscrew."

The observations made upon subject P. S. are presented in Figure 3. Gastric and colonic motility are represented schematically; the height and frequency of individual wavelike contractions are shown by vertical lines, and more sustained contractions are indicated by the shaded areas. Samples of the actual

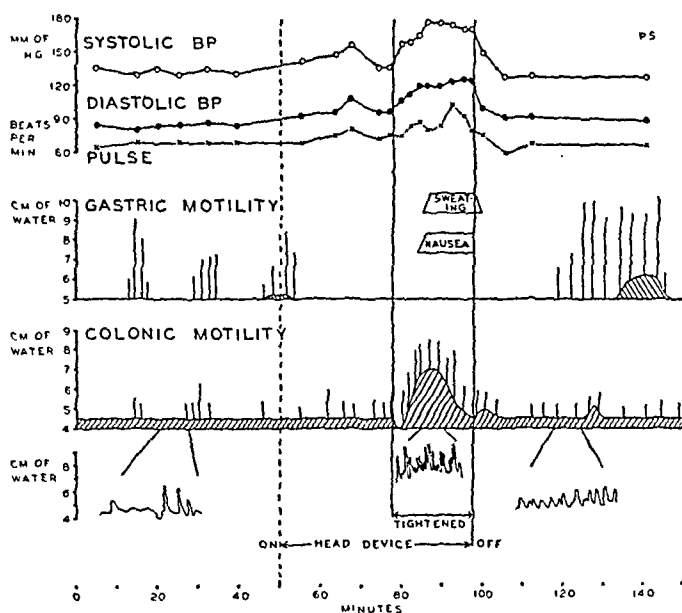


FIG. 3. Changes in colonic and gastric motility during self-inflicted experimental headache. Motility represented schematically in central panels. In lowest panel are excerpts from colonic motility tracing, oriented on scale indicating height of column in water manometer.

colonic tracing are arranged on the lowest line of the chart. During the baseline period, intermittent gastric contractions occurred, and the motility of the colon was continuous but of low grade. When the headscrew was first adjusted, gastric contractions disappeared. Colonic motility was unaffected until the actual tightening of the device and the induction of severe pain. Then a marked and sustained contraction of the sigmoid appeared, accompanied by nausea, sweating, sighing, photophobia, injection of the conjunctivae, and a marked rise of blood pressure, the maximum reading being 176/124. With the removal of the headscrew and the prompt disappearance of the pain, the colonic tracing showed a lower contractile activity, the gastric contrac-

tions reappeared, hunger appeared, the blood pressure fell to normal, sighing and sweating disappeared, and the conjunctivae lost their injected appearance. A few minutes later the subject, a conscientious, ambitious, outgoing third year medical student, revealed that during the headache he had experienced a clear cut emotional conflict, between desire for self-preservation and desire to appear as brave as his fellow students, several of whom he knew had undergone the same experience. He felt little resentment toward the experimenters; he was truly a volunteer. His attitude was rather one of self-reproach, both for his folly in volunteering and for his 'inability' to "take it."

In another student, S. W., the same experience produced physiological changes and accompanying emotional conflict which almost exactly duplicated those just outlined. Two other subjects went through the same experience without exhibiting changes in colonic or gastric function. One of these, R. W., was an idealistic intern, so devoted to the ideals of scientific investigation that the experiment, though extremely painful, had been interpreted by him as proof of his devotion to an ideal, rather than as a threat to security. The other, D. H., also failed to develop an emotional conflict. Halfway through the period of headache, he arbitrarily decided that he had had enough pain, and refused to continue to tighten the screws. He never doubted the correctness of this decision, and apparently did not care whether he appeared brave or not. His close associates described him to us as a notably decisive and stubborn individual.

### *Induced Hypoglycemia*

Eight subjects were given 15 or 20 units of insulin intravenously, and colonic motility, gastric motility and secretion, blood sugar, and signs and symptoms of hypoglycemia were observed for about two hours thereafter.

Figure 4 illustrates such an experiment in subject F. S., a 29 year old skilled laborer with a sigmoidostomy. This had been necessitated by an anal stricture, which was the result of ill advised local irradiation some months previously. The rise in colonic tonus began approximately simultaneously with the nadir of the blood sugar curve, the onset of the gastric secretory response, and the appearance of the symptoms of hypoglycemia; i.e., hunger, weakness, and hyperventilation. It will be noted that the colonic response lasted considerably longer than these phenomena. F. S. was an unusually taciturn, stoic, and undemonstrative person, who had served many times as a subject for the study of colon physiology. Despite this, and despite the only moderate hypoglycemic symptoms, he regarded the procedure as an unusually distressing experience.

Of the eight subjects, three displayed an increase in motility of the colon, but all subjects developed hypoglycemia (blood sugar less than 50 mg. per

cent). The lowest blood sugar level usually occurred 30 minutes after the administration of insulin; this varied from 11 to 44 mgm. per cent. There was no constant relationship between symptoms, blood sugar level, and gastric secretory response. Nor was there a clearcut relationship between any of these and the activity of the colon. Furthermore the attitudes and reactions of the individuals to the stressful situation (hypoglycemia) varied greatly, and often were not commensurate with the severity of the symptoms. For example, a 42 year old man whose blood sugar fell to 11 mgm. per cent had profound sweating, weakness, etc., but had no apparent change in colonic activity. A 28 year old man with a minimum blood sugar of 15 mgm. per cent had almost

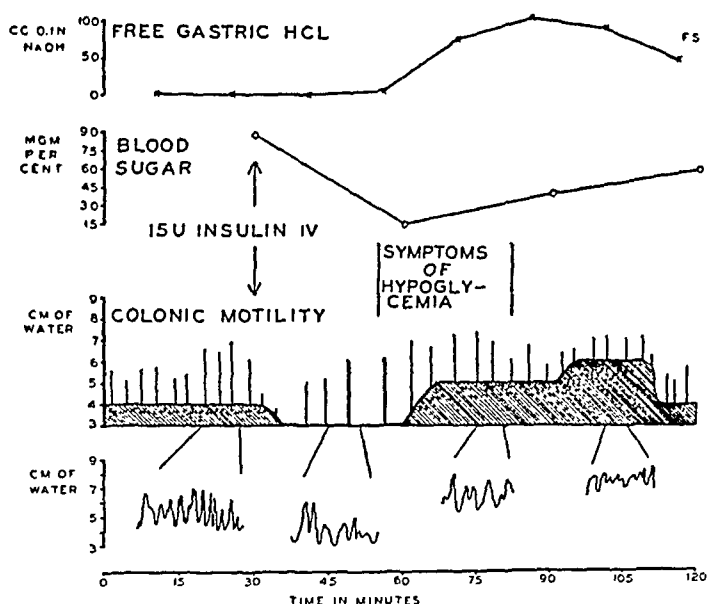


FIG. 4. Alterations in colonic motility and in gastric secretion associated with induced hypoglycemia. Representation of colonic motility as in Figure 3.

no symptoms, a marked rise in gastric acidity and motility, and no colonic response. A 34 year old woman's blood sugar fell only to 43 mgm. per cent associated with very slight weakness and hunger, but the colonic activity definitely increased. This subject was unduly disturbed by these minor symptoms.

From these observations it seems certain that increased activity of the sigmoid colon is not a specific physiologic concomitant of hypoglycemia. The hypoglycemia appeared to represent a threat to the security of four of the eight subjects; three of these developed an increase in colonic tone and activity. The four subjects to whom this experimental situation did not seem stressful had no change in colonic activity.

*Discussion of Stress-producing Life Situations*

(Eight patients with no symptoms or signs of a colonic disorder were interviewed and found to have developed emotional conflicts in the past in relation to certain stress-producing life situations.) Their colonic motility was then studied by the kymographic method. During the first hour, efforts were made to insure relaxation through reassuring and diverting conversation. The patient was then led to dwell upon the events of his life which had precipitated emotional conflict. For a time these problems were discussed either unsympathetically or without comment. At the end the patient was strongly reassured

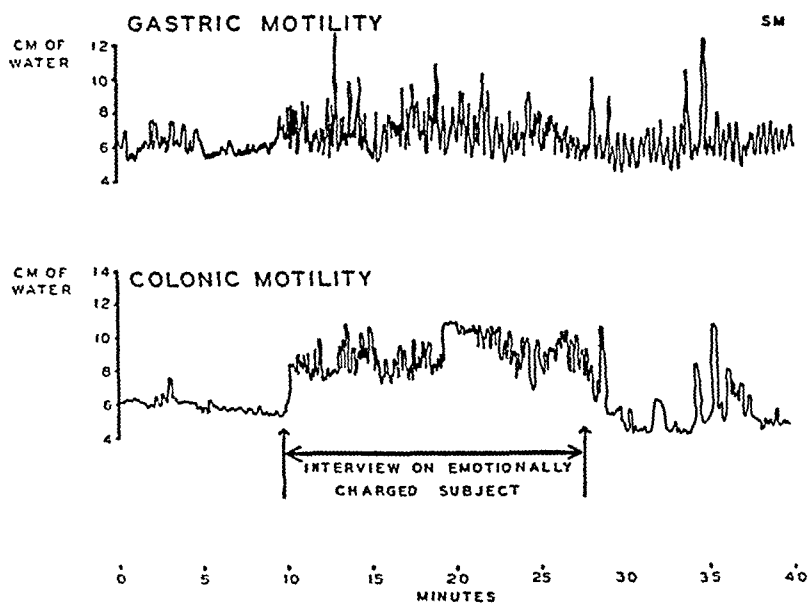


FIG. 5. Alteration in colonic motility during discussion of a stress-producing life situation. The gastric motility tracing provides a control on the effects of respiratory changes and altered intra-abdominal pressure.

and commended for the manner in which he had dealt with his troubles, and the conversation was again directed to neutral subjects.

✓An example is the study on Mr. S. M., a 53 year old tailor with hypertension (Fig. 5). He was a hard-working, conscientious man who developed strong resentments but consistently repressed his feelings. He especially resented his station in life, and had centered his hopes for future security upon his son, whom he had been maintaining in college at considerable personal expense. The son had resented his father's insistence that he obtain a college degree, and was obviously ungrateful and rebellious. ✓During the study of colonic motility, this difficult situation was discussed and interpreted by the interviewer as a disciplinary failure on the patient's part. ✓At this time colonic motility was

greatly increased, with a sustained elevation of the pressure level over the entire 20-minute period. There were no true gastric contractions, although the gastric tracing showed the effects of rapid, deep, and irregular respirations. After this interview, another and more sympathetic physician, in whom the patient had placed some confidence, entered the room and reassured him. The motility of the colon decreased at once.

In four of the eight experiments of this type, alterations in colonic motility accompanied other bodily changes and behavior patterns indicative of stress in the patient. Of the four in whom colonic changes were not observed, only one appeared to be under stress during the interview. This patient remained under evident emotional tension throughout his stay in the hospital, and we

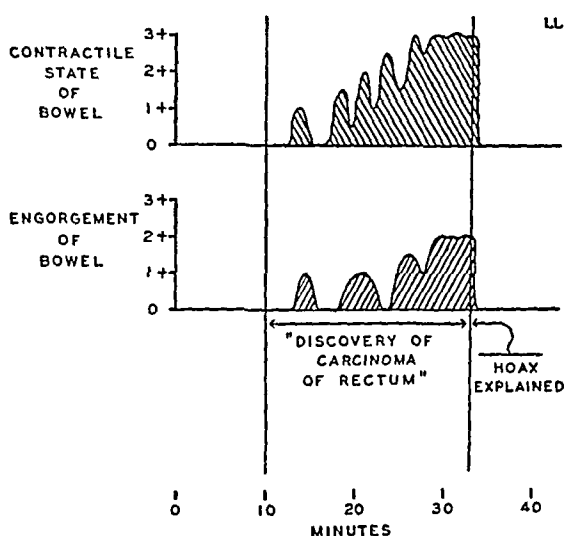


FIG. 6. Sigmoidoscopic observations during a period of baseless fear in a healthy subject (see text).

cannot be sure that he was successfully diverted and relaxed during the baseline period before the interview. There is no other apparent explanation for this inconsistency.

### *Baseless Fear Involving Special Conditioning*

Two fourth year medical students were subjected to an experiment designed (a) to evoke a baseless fear, and (b) to reflect the special experience and conditioning of the subject.

L. L. was asked to serve as subject for another experiment which would require preliminary proctoscopy. He came to the laboratory in good spirits, only mildly apprehensive, and joking about the desirability of being proctoscoped in order to be able to sympathize with patients. The instrument was inserted 15 cm., and the bowel found to be relaxed and unengorged (Fig. 6).

On pretense of waiting for spasm to relax, the area was steadily watched for 10 minutes, during which time the appearance of the colon was unchanged. After this, announcing that the "spasm" had relaxed, the examiners commenced an elaborate hoax designed to make him believe that a carcinoma of the rectum had been seen. The word "carcinoma" or "tumor" was never uttered, but the subject was questioned about recent rectal bleeding, changes in bowel habit, and loss of weight. (It was "decided" to take a biopsy, with the "reassurance" that it was probably an inflammatory lesion. With the patient in the same position, a permit for biopsy was signed, and pretense was made of actually performing the biopsy. The subject was shown a small piece of potato in a brown glass specimen bottle. By many delays the duration of the hoax was extended to twenty minutes. During this time the subject spoke in short, dry, humorless phrases, asked where the "lesion" was and for an estimate of its operability. The colon showed progressively increasing motility and engorgement, until the bowel was completely occluded. Then the nature and purpose of the hoax was explained, and the subject was given the "tissue" for his inspection. The colonic changes abruptly disappeared. The subject accepted our reassurance and disclaimed any resentment for the period of anguish he had been through. )

D. R., another student, underwent the same experience a few days later. The hoax was in so far as possible a verbatim repetition of that perpetrated on L. L. It had been arranged, however, that D. R. should hear ahead of time of the previous experiment on L. L. He was calm and cheerful throughout, and his bowel remained relaxed and unengorged even while the "biopsy" was being taken. At the end he said, "My only concern was that I should be a satisfactory control."

#### DISCUSSION

In these 45 experiments, sustained contractions of the human sigmoid colon were induced by a variety of stimuli, none of which solely and directly affected the colon. The characteristics of the stimuli are such that they seem to have only one thing in common—that they are noxious and unpleasant. The development of colonic changes was not related to the intensity of the stimulus. For example, sigmoid spasm was observed following a blood sugar level of 43 mg. per cent in one instance, and failed to appear in another subject whose blood sugar had fallen to 11 mg. per cent. The intensity of pain produced by ice water as well as by the headscrew, appeared to be relatively uniform, as judged by the reports of trained subjects, and yet colonic changes appeared only in about half of each of these groups. This fact may be related to the observation of Hardy, Wolff and Goodell<sup>2</sup> that the intensity threshold for the *perception* of pain differs from, and is usually lower than, the threshold for the



reaction to pain, as measured in their experiments by the appearance of sweat upon the skin. In our experiments, there seemed to be relative uniformity in the perception of the stimuli, but great variability in the occurrence of reactions to the stimuli.

When colonic changes were observed, they were uniformly associated with emotional tension and bodily reactions designed to protect the individual when his security is threatened—i.e., when he is under stress. In only two experiments did this general reaction to stress appear without significant changes in colonic function. (The inference is drawn that these colonic changes are a part of a general and “normal” pattern of adaptation to environmental changes regarded as threatening security.)

(The bodily reactions correlated with colonic changes included sweating and pallor of the skin, muscle tension in the neck and chest, sighing and hyperventilation, elevation of systolic and diastolic blood pressure, conjunctival injection, and reduction in gastric motility.) Further insight into the total significance of this reaction pattern was gained from study of the reactions to insulin. In these experiments the colonic changes occurred together with the manifestations of “insulin reaction,” after the lowest point of the blood sugar curve had been reached, and during the return of the blood sugar toward normal. This coincidence suggests, but does not prove, that sigmoid spasm is allied to the general homeostatic mechanisms by which the organism adapts to an unfavorable environment.

(The coincidence of sigmoid spasm and nausea had been noted in our earlier experiments.<sup>1</sup> Wolf<sup>2</sup> had shown that nausea is regularly associated with the disappearance of spontaneous gastric contractions.) (It was therefore anticipated that gastric motility would be found to decrease during significant increases in sigmoid motility.) These findings are in accord with those of Cannon,<sup>4</sup> who studied the intestinal motility of unanesthetized cats under the stress of being tied down and threatened by growling dogs, and found a reduction of motility in all segments of the bowel except the distal colon. (In patients with spastic constipation and proctoscopically visible sigmoid spasm, hypofunction of the stomach is often indicated by epigastric fullness, belching, nausea, vomiting, and hypochlorhydria.) It is conceivable that these phenomena, so common in clinical practice, are part of the general reaction to stress.)

There were in these experiments many striking correlations between sigmoid spasm and distinct emotional conflicts. The occurrence of somatic changes was related to the attitude of the subject toward the noxious stimulation. Even with as formidable a device as the headscrew, sigmoid spasm appeared only when the experience precipitated an emotional conflict. The painful immersion of the hand in ice water produced a colonic reaction when the subject was in doubt as to the safety of the procedure. Subsequent immersion of the same

hand of the same subject in water at the same temperature produced the same degree of pain, but no stress and no colonic reaction. The only obvious change had been in the attitude of the subject, who no longer feared the experience.

✓The importance of the attitude of the subject in determining his bodily reactions is further indicated by the occurrence of colonic spasm during simple discussion of stress-producing life situations. Some patients, who had become partially adapted to their problem or who had been strongly reassured about them by their physicians, failed to develop emotional reactions or colonic changes when these problems were discussed. The feelings of others were such that even the discussion of their life situations was regarded as a threat to security. These patients reacted with the same bodily mechanisms as those used by others beset by physical stimuli.

✓The attitude and conditioning of the subject again played a role in the reactions of the two medical students to the supposed discovery of a carcinoma of the rectum. ✓Here the stimulus was a complicated pattern of words and actions, ordinarily used only when the physician tries to perform necessary services for the patient with cancer without unduly alarming him. To the patient ignorant of medical matters, the physician's behavior is usually not alarming, and not productive of colonic spasm. The conditioning of physicians and fourth year medical students is such that questions about rectal bleeding and the taking of a biopsy through the proctoscope are symbolic of cancer of the rectum and of its consequences, and hence stress-producing. Thus it was not unexpected that one of our subjects would develop spasm and engorgement of the sigmoid, or that the other, who knew it was a hoax, would develop no changes. These findings suggest specifically that the symptoms of "cancerphobia" may stem not only directly from the imagination of the patient, but also from alterations in bodily function which are the expected accompaniments of emotional tension. Under these circumstances, the most direct and potent therapeutic device available to the physician is strong reassurance based upon thorough clinical study.

The occurrence of sigmoid spasm in response to a wide variety of noxious stimuli, and its association with changes in blood pressure, respiration, peripheral blood flow, and the like, indicate that it is a reaction of value in the protection of the organism. (The observation of Cannon<sup>4</sup> that the movements of the stomach and upper intestine cease during strong emotion has been interpreted as the economy of the body in suspending functions not needed during combat. The contraction of the sigmoid colon may be regarded as preventing feces from entering the rectum and initiating the reflexes of defecation during periods of emergency. The occurrence of diarrhea under stress may be associated with failure of development of sigmoid spasm.)

Heightened contractility of the sigmoid colon may thus be useful in the total

mobilization of the animal for fight or flight. Its value to a person beset by cold pain, headache, hypoglycemia, or disturbing conversation is probably much less, and its occurrence must then be due to the calling forth of a primitive pattern of adaptation, inappropriate to the needs of the individual. This inappropriate reaction has been present in these experiments only when the individual felt his security was threatened. We infer from this that it is not directly related to the environmental stimuli, but rather to the subject's interpretation of these stimuli. (In this view, the occurrence of sigmoid spasm and constipation in neurotic patients with mucous colitis may represent similar reactions of the individual to an environment regarded by him as stressful. Experimental studies of these reactions in patients are being carried on and will be reported later.)

#### SUMMARY

In 45 experiments on 39 subjects who had no clinical disorder of the colon, the functional state of the sigmoid colon was studied either by proctoscopic observation or by inlying balloons. When subjected to cold pain, compression of the head, hypoglycemia, or the discussion of troublesome life situations, about one-half of these persons exhibited marked increases in the contractile state of the sigmoid colon. In all of those who reacted thus, there were associated bodily changes and emotional reactions which indicated that the person was under stress. Of those whose sigmoid colon did not react, only two gave evidence of a general reaction to stress. With all four experimental stimuli, the colonic response of the subject seemed to be related to his attitude toward the stimulus: *i.e.*, it occurred only when the stimulus was regarded as a threat to security.

#### CONCLUSION

Spasm of the sigmoid colon occurs in healthy persons when they are under stress induced by experimental stimuli. The appearance of this reaction depends not only upon the stimulus but also upon the subject's interpretation of the stimulus.

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## ALTERATIONS IN COLONIC FUNCTION IN MAN UNDER STRESS

### III. EXPERIMENTAL PRODUCTION OF SIGMOID SPASM IN PATIENTS WITH SPASTIC CONSTIPATION\*

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#### INTRODUCTION

In previous reports<sup>1, 2</sup> it has been shown that healthy persons may exhibit spasm, engorgement, and excessive mucous secretion in the sigmoid colon when under stress induced by experimental procedures. These colonic changes were observed during severe pain, during induced hypoglycemia, and during the discussion of unpleasant life situations productive of emotional conflict. These experiments presented many similarities, both in the colonic changes and in the pattern of the emotional conflicts, to common clinical experiences with patients with "irritable colon" or "spastic constipation."

It has long been considered that the typical patient with spastic constipation is sensitive and immature, and adapts with difficulty to environmental stress. The onset and exacerbations of his illness have been found by White, Cobb, and Jones<sup>3</sup> to coincide with some difficult life situation which engenders an emotional conflict involving anxiety, resentment, and guilt. The constipation and lower abdominal pain which occur at such times have been related to spasm and hypermotility of the distal colon. Spasm of the sigmoid, together with excessive mucous secretion and mucosal engorgement, is usually visible at proctoscopy. These findings have become the most commonly accepted objective evidence of spastic constipation.

In the experiments here reported, we have studied the changes in motility of the sigmoid colon in patients with spastic constipation during stress induced by experimental procedures. Our purpose has been to determine whether these colonic reactions are similar to those found in clinical observation of these patients, and to those produced in healthy persons under similar experimental stress.

#### PROCEDURE

The methods of study were similar to those previously described by us:<sup>1, 2</sup>

(a) The lower sigmoid colon, 12 to 22 cm. from the anus, is continuously observed through the proctoscope, with the patient in the left lateral position. The contractile state of the bowel and the engorgement of its mucosa are graded as zero to four plus on arbitrary scales.

\* Supported in part by generous gifts by John L. Given, Minnie H. Butt and Marie and John Zimmermann.

(b) A distensible latex balloon is passed through the proctoscope to a point 20 to 40 cm. from the anus, and the pressure changes are recorded continuously on a kymograph, utilizing a water manometer. The subjects remain supine upon an examining table throughout the experiment.

The subjects were ambulatory patients who had complained of constipation or of colonic pain; patients in whom diarrhea was a prominent symptom were excluded. In all a diagnosis of spastic constipation had been made. This was based upon failure to find relevant organic disease by physical examination, proctoscopy, roentgenologic and parasitologic study; and upon recognizable coincidences between the onset or recurrence of bowel symptoms and life situations productive of emotional conflict. The patients were selected solely for the clarity with which these coincidences could be understood.

All subjects were prepared by repeated enemas of physiological saline, and by omission of the previous meal. During the experiments, they were encouraged to express their feelings freely and to report all bodily discomfort. Despite this, there was little expression of hostility toward the investigators, and few patients reported colonic pain during the experiments. At the end, each patient was asked to review carefully his emotional reactions to each stage of the experiment.

The stimuli used were (a) immersion of the hand in ice water at 0 to 1 degrees Centigrade for five minutes or longer; (b) compression of the head with an adjustable steel band containing rubber-cushioned screws, which produces a severe experimental headache; (c) hypoglycemia induced by intravenous insulin; and (d) the unsympathetic discussion of life situations known to be disturbing to the patient, and associated in time with the development of spastic constipation or colonic pain.

## RESULTS

### *Cold Pain*

Six patients experienced severe cold pain as the result of immersing the right hand in ice water. In all but one intense pain began about 1 to 1½ minutes after immersion was begun, and began to disappear after five minutes even though the hand remained in the water. These patients described their pain in highly colored terms, and gave vent to their distress in squirming movements of the body, in involuntary cries, or in moaning. All these exhibited increased motility of the sigmoid colon. In three cases this was recorded kymographically. In two it was observed by proctoscopy; engorgement of the mucosa and excessive mucous secretion were also seen. In three patients these colonic changes persisted after the removal of the hand from the water; these three described unpleasant tingling and burning sensations in the hand, which

quite clearly distressed them. In two the colonic hypermotility subsided, together with the pain and general anxiety, before the hand was removed. The sixth patient refused to keep her hand in more than two minutes, and developed only a minor and transient increase in the motility of the sigmoid.

### *Headache*

One patient endured a severe experimental headache lasting twenty minutes. The sigmoid colon was continuously observed through the proctoscope for 30 minutes before the stimulus, during which time the initial occlusive spasm disappeared and the lumen became widely patent. Within five minutes after the beginning of the headache, occlusive spasm reappeared, and was continuously present until after the band was removed from the head. There were no significant changes in the engorgement of the mucosa. The patient described his distress in vivid terms, and exhibited restless movements, hyperventilation, groaning, and belching.

### *Hypoglycemia*

The sigmoid motility of three patients was studied kymographically before and for two hours after the injection of 15 to 25 units of regular insulin intravenously. This sufficed to reduce their blood sugars from fasting levels of 82, 90, and 100 mg. per cent to 21, 54, and 36 mg. per cent respectively, followed by a return to or toward the fasting level within two hours. One patient exhibited marked weakness, sweating, and restlessness, but the others had no symptoms of hypoglycemia. None developed a significant alteration in the record of colonic motility.

## DISCUSSION OF LIFE SITUATIONS EVOKING EMOTIONAL CONFLICT

During continuous observation of sigmoid motility by proctoscopic or kymographic methods, 29 patients were interviewed and led to discuss events of their lives which were already known to be disturbing to them and to have been associated in time with the onset or exacerbation of colonic symptoms. In 12 patients, significant alterations in colonic function were observed during the stress of the interview. The following individual case studies will serve to illustrate our procedure and the changes in colonic motility observed.

*Case 1.* A 37 year old German housewife, who had been found to have spastic constipation and essential hypertension, was subjected to prolonged proctoscopic observation (Fig. 1). During a baseline period of 26 minutes the conversation was directed to a discussion of knitting, her favorite leisure-time occupation. The patient appeared relaxed and cheerful; the sigmoid was minimally engorged and had a wide lumen, except for transient spasm and engorgement when she spontaneously lamented her inability to bear children. Following this the patient was led to discuss

the hardships of her starving relatives in Germany, and the question was raised whether she had helped them to the limit of her ability. She appeared anxious and defensive, and her colon exhibited occlusive spasm and marked engorgement, with associated rise in blood pressure from the baseline level of 140/110 to a peak of 170/130. She was then comforted by the interviewer, and commended for having done well by her family under trying circumstances. She quickly resumed her composure. The blood pressure returned to its initial level, and the spasm and engorgement of the colon rapidly decreased. After an interval of quiet, the patient spontaneously expressed resentment over her husband's ability to have regular bowel movements. The colonic changes then reappeared, and the observations were concluded.

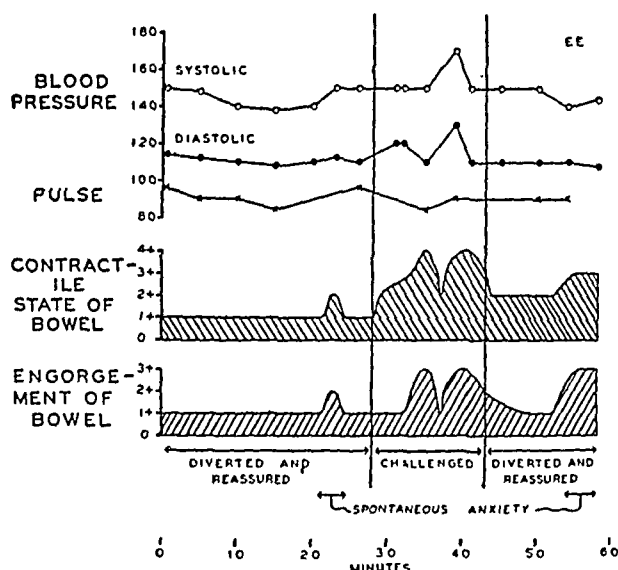


FIG. 1. Case 1. Circulatory and colonic changes in a patient with spastic constipation during discussion of a stress-producing life situation (continuous proctoscopic observation).

*Comment.* In this patient, heightened contractility and mucosal engorgement of the sigmoid colon were observed in association with evident emotional tension. These changes appear to have been induced by deliberate discussion of a difficult life situation, which had been associated with exacerbation of the patient's symptoms.

*Case 2.* A 26 year old scenery designer complained of epigastric pain and lower abdominal cramps. During a kymographic recording of colonic motility (Fig. 2) 25 units of regular insulin was injected intravenously, and his blood sugar and free gastric acidity were repeatedly determined over a period of two hours. During this time the patient was relaxed and drowsy. His blood sugar fell to 36 mg. per cent. Although the free hydrochloric acid of his gastric contents rose to 130 units, he developed no feelings of distress, no symptoms of insulin reaction, and no alteration of colonic motility. At a time when the blood sugar had returned to normal, the patient was





This suggests that the subjective interpretation of the stimulus may be more important in the production of colonic change than its potential danger.

*Case 3.* A 57 year old American born white woman complained of severe constipation for 36 years. This gradually became refractory even to strong cathartics and enemata, and was associated with pain in the right lower quadrant, abdominal distension, epigastric distress, and nausea. She also suffered from severe migraine, dysmenorrhea, and uterine myomata. No organic cause for her constipation was found on physical examination, proctoscopy, barium enema and GI series, and parasitological examination of the stool.

The patient was one of five children of a kindly and stable mother and a hypochondriacal, fear-ridden, neurasthenic father, who dominated the household by various neurotic stratagems. Of the four siblings, one is disabled with advanced tuberculosis, one is severely neurotic, and one is confined in a mental institution because of a psychosis. The patient was a "nervous" child, and was enuretic until the age of nine.

When the patient was 21 her father died suddenly. Shortly afterward she left the family fold and married a man whom she soon discovered to be her intellectual and cultural inferior. Her severe constipation began at this time. The marriage was never satisfactory, although the patient had one child. After 17 years she separated from her husband. Following this she developed increasing anxiety, restlessness, and fear, and sought solace in a religious cult run by a "Metaphysical Healer." She repeatedly received temporary symptomatic relief from this "healer". For example, she would sleep well and cease to vomit after hearing his voice over the telephone. Two years before, it had fallen to her lot to commit her sister to a mental institution because of a severe depression.

After her clinical examination, the motility of her sigmoid colon was studied. Proctoscopy showed the lumen to be occluded by spasm; the mucosa was dry but markedly engorged. A balloon was introduced to a point 25 cm. from the anus, and its position in the sigmoid was confirmed by fluoroscopy. The tracing was begun with the patient lying quietly upon the table. Despite reassurance, she at first appeared tense and apprehensive, and sighed repeatedly; later she became outwardly calm. The initial high contractions on the record are in part due to bowel motility, and in part to sighing.

At point "A" (Fig. 3) the examiner reentered the room and began a discussion on ostensibly neutral topics. She spontaneously shifted the subject to her symptoms, and at point "B" began to speak of her father. She revealed that she had feared and disliked him during her childhood and blamed him for much of her nervousness, implying that she identified her own personality with his. Despite this evident hostility, she had sympathized with his neurotic attitudes and his tendency to dominate the family. It was evident also that his sudden death had been profoundly upsetting to her and accompanied by strong feelings of guilt on her part. During this period her manner, her voice, and the content of her speech indicated the poignancy of her emotions, and the colonic tracing showed repeated high contraction waves, associated with abdominal cramps.

At point "C", having mentioned her despair at ever overcoming her symptoms, she began to tell about her religious experiences. Abruptly her manner changed. Her eyes became moist, her voice quavered and became faint, and her attitude became that of a credulous and thankful child. She indicated that her adherence to the cult had given her great aid in carrying her feelings of guilt and unworthiness, and that it had become her one real source of dependent emotional security. During this period the colonic contractions were smaller even than in the baseline period. At "D" she began to speak of how her father might have benefited from the cult. Her manner

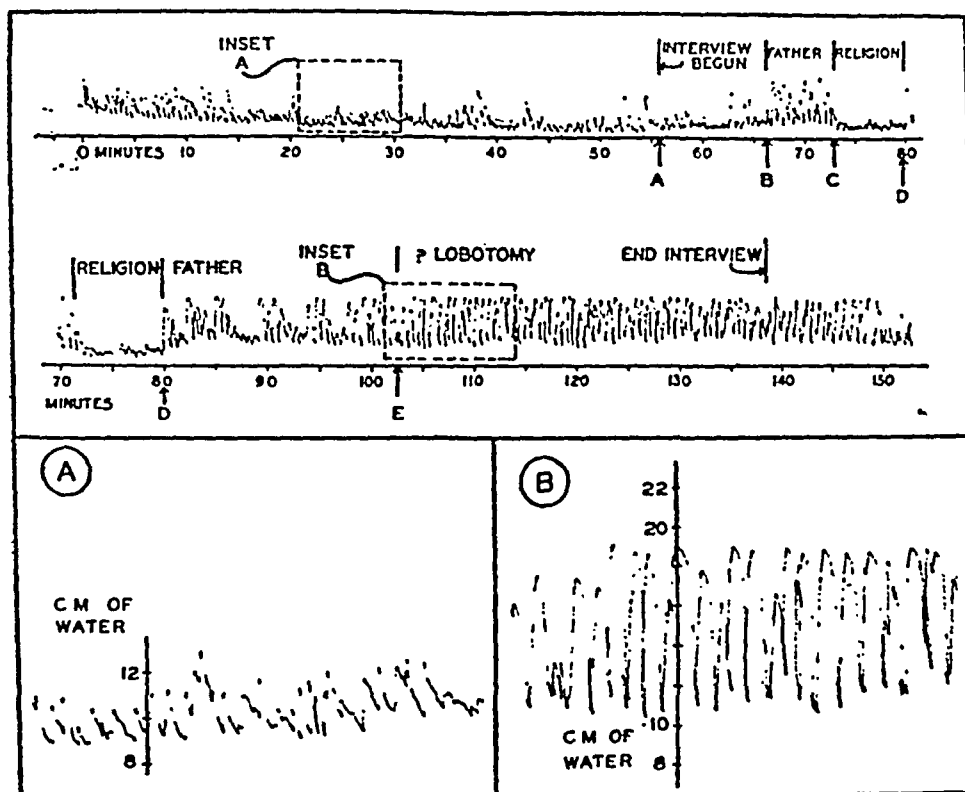


FIG. 3. Case 3. Kymographic record obtained from sigmoid colon during extensive interview with a patient with spastic constipation (see text).

and voice again became hostile, and the pattern of high colonic contractions abruptly reappeared.

After this point, despite efforts to turn the conversation to subjects which were less distressing to her, she persisted in returning to her present problems, and displayed intermittent anxiety and hostility. Finally at point "E" she entered upon a prolonged discussion of her most pressing dilemma—whether to allow a prefrontal lobotomy to be done on her psychotic sister. Her resentment toward her sister and her guilt feelings over her own actions could be detected with ease. From this point outwards she maintained high colonic contractions without intermission until the end of the tracing, some minutes after the discussion had been concluded.

*Comment.* Heightened motility of the sigmoid colon in this patient took the form of unremitting contractions of large amplitude. This pattern ap-

peared whenever the patient dwelt upon situations which she had regarded with conflicting attitudes of resentment and guilt.

*Case 4.* Mrs. M. F. was a 48 year old Irish-American housewife who had had severe spastic constipation since childhood. In the preceding three months her condition had become worse. She would fail to move her bowels, even with laxatives, for two weeks at a time, and she was troubled with nausea, epigastric distress, and belching. Physical examination yielded no pertinent findings, and proctoscopy was negative. Barium enema revealed a failure of rotation of the cecum, but there was no evidence of obstruction or other structural defect as basis for constipation.

The patient was the eldest of three children of impoverished Irish Catholic parents, who lived on New York's lower East Side. When the patient was five years old, her mother died in childbirth. She grew up in an orphanage and later became an obstetrical nurse. She had been married for 23 years to an Irish policeman, and had six children. The eldest, Helen, had always been selfish, rebellious, and asocial. In March, 1947, Helen announced that she intended to marry a man of whom the patient disapproved. This was soon followed by an exacerbation of the patient's symptoms, and by her first visit to our clinic.

A motility study was performed with the sigmoid balloon placed 30 cm. from the anus. The patient first rested quietly, sometimes dozing, for one hour. A constant level of basic tonus was maintained (Fig. 4), with many superimposed contractions 1 cm. in height, and less frequent (every 3-10 minutes) major contractions of 4-6 cm. amplitude and 1-2 minutes' duration. The patient was then awakened and engaged in conversation. During discussion of her household routine and of the good qualities of her husband, there was no significant change in the motility of the sigmoid. The patient spoke in a moderately tense and spirited manner, and respiratory irregularities were reflected in the tracing.

The behavior of her daughter Helen was then reviewed in an intentionally unsympathetic manner. The patient announced that she had dealt with the problem satisfactorily by refusing to permit her to be married, and defended her decision calmly against any suggestion that it might not have been wise. There was no change in her manner or in the tone of her voice, and the character of the colonic tracing was unchanged.

The patient then spontaneously began to talk of her husband's unreasonable restrictions upon her, and of his recent habit of getting drunk on Saturday nights. (She later said that she had never before discussed this problem with anyone.) This had not resulted in family disgrace, in financial hardship, or in verbal or physical abuse directed at herself. When asked why she was alarmed by his minor degree of alcoholism, she answered, "I guess I don't want him to end up like papa." She then revealed for the first time that her father had been a chronic alcoholic, and had neglected her and her siblings both before and after the death of her mother. She attributed her mother's death to inadequate prenatal care, in turn due to her father's alcoholism. She described with considerable bitterness having been taken off to the

orphanage by an uncle who was a priest. Her main objection to Helen's erstwhile fiancé, she added, was the fact that he was known to drink. During these revelations the patient was agitated, flushed, and hurried in her speech. She could not be led to other topics of conversation, and the interview ended without reassurance. The baseline of the colonic tracing had risen steadily to a level 5 cm. higher than that during her period of relaxation. Major individual contractions were less frequent. When the examiner reentered 17 minutes later and ended the recording, the patient still appeared tense and shaken, and the level of intracolonic pressure had not fallen.

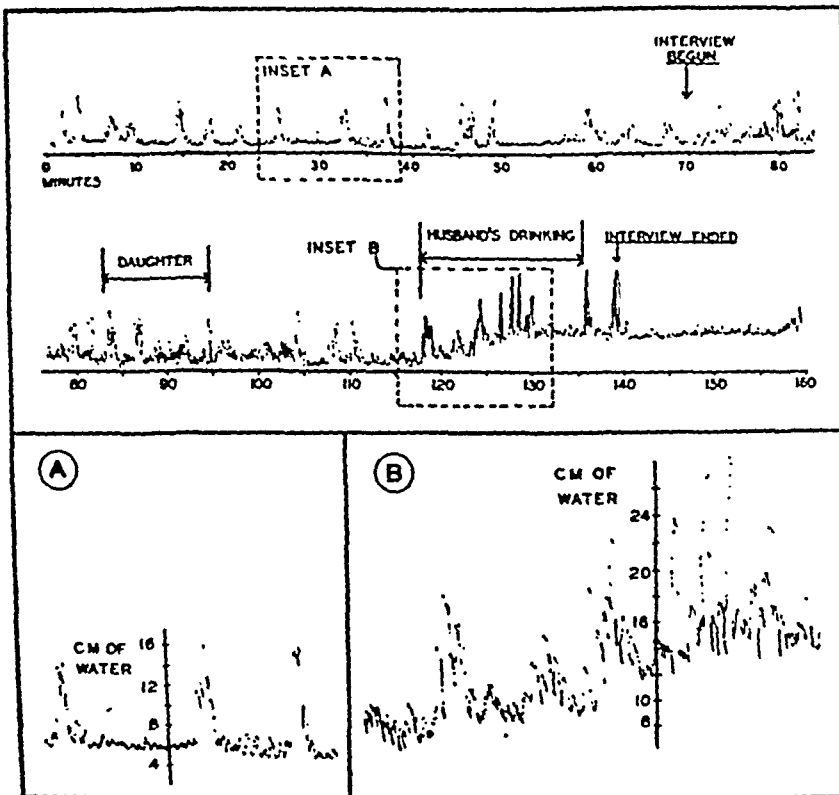


FIG. 4. Case 4. Intermittent wavelike activity of colon in patient with spastic constipation during period of relaxation. Sustained spasm developed during period of discussion of emotionally charged subject.

*Comment.* Prior to this experiment, the patient had discussed the behavior of her daughter with great agitation and finally with tears. In the meantime she had dealt with this problem constructively. Now discussion of it did not disturb the patient's composure, and the motility of her colon was unaffected. A few minutes later, the revelation for the first time of an unresolved problem (her husband's alcoholism) was accompanied by a show of profound emotion. At this time there was intense and prolonged colonic spasm.

## DISCUSSION

The subjects of these experiments had experienced constipation or colonic pain when faced by stress-producing situations in their own lives. At such times they presumably developed spasm and hypermotility of the distal colon. In most of the subjects sigmoid spasm had been visible during proctoscopic examination in the clinic. In most of them the motility of the sigmoid colon approached normal during periods of calm under laboratory observation, but was again greatly increased when they were exposed to experimental stress.

The magnitude of the changes observed requires some comment. In subjects observed proctoscopically, the degree of spasm which occurred during experimental stress was comparable to that seen on routine proctoscopy in patients severely ill with spastic constipation. The mucosal engorgement was greater than that seen following a soapsuds enema. During 18 months' experience with kymographic recording of sigmoid motility, no spontaneous increases in motility have been found to approach those obtained during experimental stress, and no autonomic drug has produced effects exceeding these in magnitude.

It was at first surprising to us that many patients with spastic constipation should display vigorous wavelike activity of the sigmoid colon, and in particular that stimuli productive of constipation should augment this activity rather than depress it. The apparent contradiction is further enhanced by the finding<sup>4</sup> that the sigmoid contractions in patients with diarrhea are less vigorous than in patients with constipation or in healthy persons. By the use of tandem balloons, however, we have discovered that almost all of these contractions occur simultaneously at two points in the sigmoid, and are hence probably non-propulsive in nature. This would serve to confirm in part the observations of Adler, Atkinson and Ivy<sup>5</sup> on the spontaneous motility of the descending colon in patients with colostomies. They reported that the majority of the colonic waves were non-propulsive.

In the majority of these experiments on patients with spastic constipation, the stimulus was not a tangible one, not a physically painful or shocking experience, but the mere discussion of life situations known to have produced emotional tension in the patient. The relative potency of such a stimulus as compared with moderately severe hypoglycemia is attested by the experiences recorded in Case 2.

A word should be said about the variability of the results when patients were stimulated by a discussion of personal problems. Under the conditions of the experiments these patients were reacting to several aspects of their immediate environment, of which the most important can be enumerated thus:

- (1) The experimental procedure is in itself unfamiliar and unpleasant, and some patients could not overcome their initial apprehension.

(2) There were often distracting occurrences in the examining room. Each move made by the physician, even his entry into the room, could in this strange setting be laden with connotations for the patient, and reflected in changes in the kymographic record. The more recent studies have been conducted in a small, quiet room with a minimum of visible laboratory equipment and a minimum of interruptions from other persons. In this way, disturbances of this kind have been reduced.

(3) The attitude of the patient toward the interviewer has been a significant factor. Hostility toward the interviewer may negate his attempts to reassure the patient, and a feeling of dependence upon the interviewer may make it virtually impossible for him to induce experimental stress in the patient.

(4) The patient's unexpressed feelings, conscious or unconscious, may override the effect of the topic of discussion.

It is only when these disturbing factors have been reduced to a minimum that the topic under discussion becomes the major stimulus. This, we think, explains why so many of our earlier observations were "negative."

The stimuli presented to these patients were identical with those previously used in experiments upon persons without clinical evidence of colonic dysfunction. Although some of the healthy subjects given insulin intravenously developed colon spasm, no one of the three patients with spastic constipation did so. In all other respects the colonic reactions of the two groups to our experimental stimuli have been essentially the same. In both groups, the pattern of the colonic reaction was the same with all the experimental stimuli. In both groups the colonic changes occurred only in association with other bodily changes or with evident emotional reactions which indicated that the subject was under stress.

Thus both healthy persons and patients with spastic constipation have been seen to develop the same colonic changes when under stress. Yet only in the patients does clinically significant dysfunction of the colon occur. We infer that this dysfunction is not due to a specific "abnormal" pattern, but rather to greater intensity and greater duration of the same reactions seen in healthy persons. The exaggeration of these functional changes is probably due to the occurrence of more prolonged stress in the patient than in the average healthy individual. Occasionally, stress in these patients takes the form of unusually severe and sustained physical hardship or personal tragedy which is obvious to the medical observer. More often the patient is under stress, in spite of a reasonably favorable life situation, because his neurotic traits lead him to see in that situation something which threatens his security. These individuals may be considered as almost constantly reacting to the dangers *they and they alone perceive* in their environment. The attitudes of these persons toward their environment may be the result of unconscious drives which stem from remote and unpleasant experiences in childhood. The significance to the patient

of a particular life situation may thus not be clear until the personality of the patient has been thoroughly studied.

We conceive, therefore, that the seat of disorder in spastic constipation is not in the bowel, but in the environment and in the patient's attitude toward his environment. This concept is at variance with previous ideas concerning this disorder, crystallized in such names as "unstable colon" or "colonic neurosis." These terms are unsatisfactory in that they locate the fundamental disturbance in the bowel, and suggest that the disorder is limited to the bowel. Yet most patients exhibit other clinical manifestations of bodily disorder, such as sweating of the hands, headaches, nasal discharge, and hypertension. These and other bodily changes were observed in our experiments as concomitants of sigmoid spasm. Our concept is also incompatible with certain hypothetical mechanisms held to be active in this disorder—"autonomic imbalance," or "neuromuscular dysfunction." We object to these terms in that they suggest that the bodily mechanisms in the patient are in themselves abnormal, whereas in our experiments they have been found to be strikingly similar to those observed in healthy persons. Whatever the neural and humoral mechanisms by which they are produced, we believe that these reactions of the colon are part of a "normal" and generalized bodily reaction to stress.<sup>6</sup>

We find in these results certain therapeutic implications. Evidence has been presented that the colonic mechanisms in patients with spastic constipation are not qualitatively abnormal. It is therefore unlikely that continued attempts to alter these mechanisms by diet and drugs will prove useful. Because the essential characteristic of these patients appears to be that they are often under stress, the therapeutic energies of the physician might better be directed toward the reduction of that stress. The physician commonly modifies the environment of the patient temporarily when he admits him to the hospital for diagnosis or sends him on a much-needed vacation. More fundamental and lasting changes depend upon better understanding by the physician of the factors productive of emotional tension in the individual case. The services of the medical social worker may be useful in bringing about more favorable conditions.

The physician commonly modifies the patient's attitude toward his environment by listening sympathetically to his complaints and allowing him to ventilate his feelings. Further improvement can be achieved by reassurance as to the absence of organic disease and explanation of the illness as a bodily reaction to stress. The patient soon learns from experience that stress-producing situations are associated with an exacerbation of symptoms. Fortified by the physician's understanding of his problem, he may learn to face these situations more philosophically.

Although much benefit can be obtained by the early use of these simple psychotherapeutic measures, it is a lamentable fact that they are often ineffective in patients who have relied upon injudicious medication for long periods. In such patients, and in those whose major emotional conflicts cannot be reached on a conscious level, treatment by a psychiatrist is invaluable, and in view of the degree of total disability, often economically justifiable.

#### SUMMARY

In 39 patients with spastic constipation or colonic pain, the motility of the sigmoid colon was studied by proctoscopy or by inlying balloons. When subjected to cold pain, painful compression of the head, or the discussion of life situations productive of emotional conflict, these patients often exhibited markedly increased motility of the colon. This change was associated with obvious changes in speech or in behavior indicating that the patient was under stress. These results are similar to those earlier obtained with persons who had no clinical disorder of the colon.

#### CONCLUSION

Spasm of the sigmoid colon may occur in patients with spastic constipation as part of a general bodily reaction to nonspecific stress. The fundamental abnormality in the patient with spastic constipation lies not in the behavior of his colon but in his susceptibility to stress-producing life situations.

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## THE THIAMINE EXCRETION TEST AS A GAUGE OF DIETARY ADEQUACY\*

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In a previous communication<sup>1</sup> we reported the results of blood assays of certain vitamins in a series of 100 consecutive unselected hospitalized patients. These results demonstrated that the determination of blood levels of the vitamins investigated did not offer a means of determining dietary adequacy, and thus could not be used as an objective method for diagnosing clinical dietary deficiencies.

The study herein described was undertaken in a further effort to evaluate methods for quantitatively demonstrating dietary inadequacies, and thereby so-called sub-clinical deficiencies. Until diagnostic criteria are more clearly defined, preferably by the development of laboratory methods for measuring the *degree* of nutritional failure, therapy with nutritional supplements will remain unsatisfactory. That it is, at present, unsatisfactory is borne out by the wide divergence of opinion as to the importance of vitamin supplementation. The enthusiasts see deficiency states in essentially every new patient, while the skeptics will not prescribe unless the patient has a frank deficiency syndrome. This study was undertaken to determine whether the fraction of a given dose of thiamine injected intramuscularly which is excreted in the urine, could be correlated with the dietary habits of the individual.

### METHODS

Fifty unselected consecutive hospitalized patients were used as subjects for the study. None of these patients were acutely ill, none presented clear-cut indications of avitaminoses, and the majority were hospitalized because of symptoms referable to the gastrointestinal tract. On the first morning after admission to the hospital and while fasting, a two-hour urine specimen was collected to determine basal thiamine excretion. One milligram of thiamine hydrochloride was then administered intramuscularly and the urine for the succeeding four hours was collected and assayed for thiamine. The fraction of the total 1 milligram dose of thiamine excreted in the four-hour period was calculated after correcting for the basal thiamine excretion. Friedemann's<sup>2</sup> method was used for the determination of thiamine.

On the basis of a diet history taken on each of the patients, and extending

\* This study supported in part by a grant from The Wander Company.

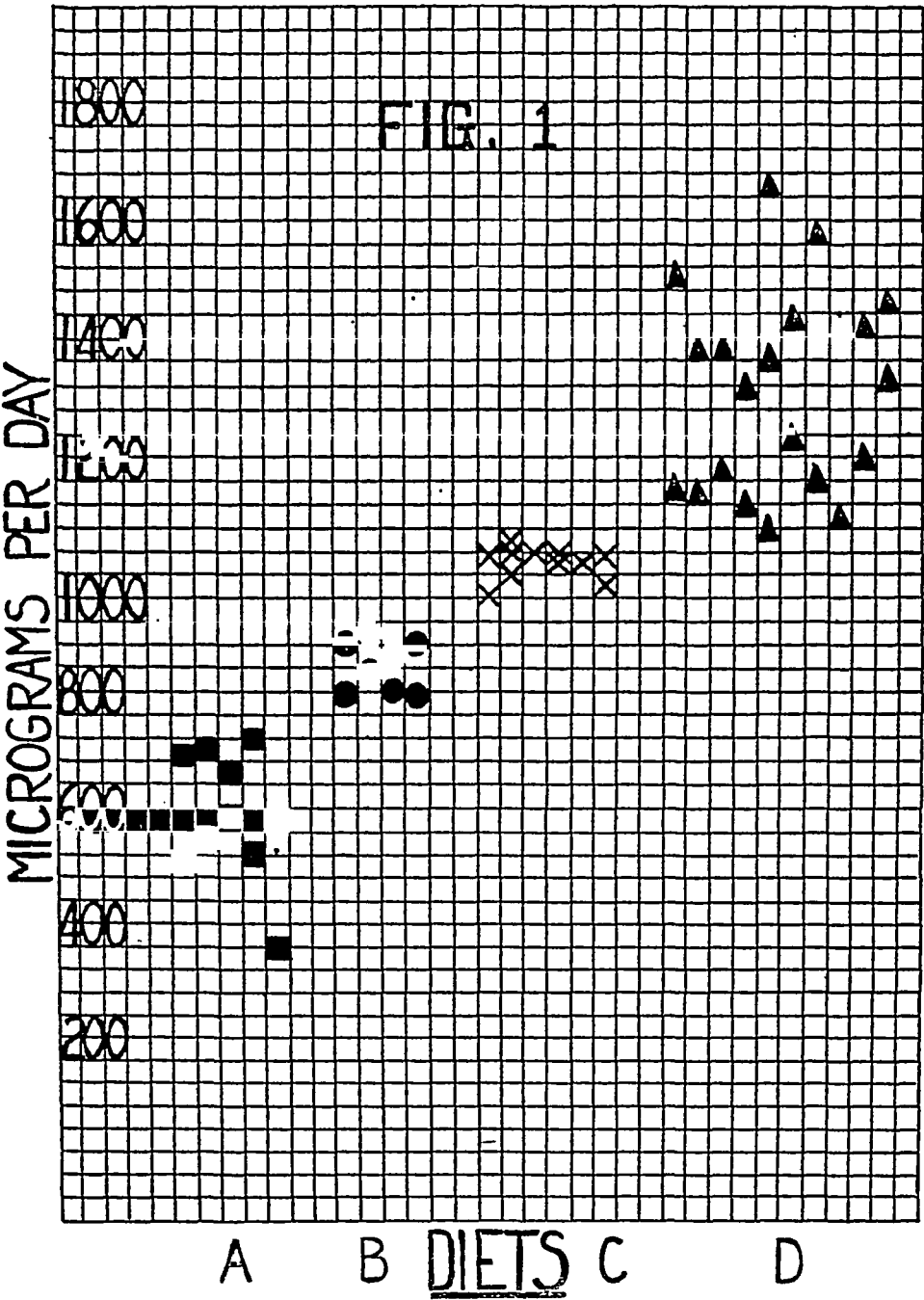


FIG. 1. Distribution of patients with respect to estimated thiamine intake.

back over a period of years in most cases, the patients were divided into one of four arbitrarily selected categories. The distribution of the patients between the various categories is shown in Figure 1.



that among the patients in Group D the thiamine intake averages almost three times as much as that among the patients in Group A. In Figure 2 is shown the distribution of the patients with respect to the fraction of the injected thiamine excreted in the urine. It is apparent that there is a complete lack of correlation between the estimated thiamine intake and the tendency of the tissues to make use of this dose of parenterally administered thiamine.

#### DISCUSSION

Since the majority of the patients studied had been limited in their dietary intake as a result of chronic illness, usually referable to the gastrointestinal tract, it is not surprising that the thiamine intake in the case of most of the patients was relatively low. However, the difference between those included in Group A as compared with those in Group D is so great that it must be concluded that, in view of the complete lack of correlation between the quality of the diet and the fraction of the injected thiamine excreted, this test would be valueless in determining dietary adequacy. It also seems safe to conclude that the test would be valueless as an aid in diagnosing subclinical deficiencies since even though the "diet history" method of estimating thiamine intake is crude, there inevitably would be a higher percentage of patients suffering physically from dietary failure in Group A than in Group D.

The possibility that all except the two patients with high percentage excretion showed greater than normal tissue retention of thiamine because of a sub-optimal thiamine intake, is of no importance since irrespective of this possibility the results illustrate clearly that the test will not distinguish between degrees of deficiency.

#### SUMMARY

The fraction of a one milligram dose of thiamine hydrochloride injected intramuscularly which was excreted in the urine in a four-hour period was determined in fifty consecutive, unselected, hospitalized patients, who had been grouped into one of four categories depending on their average thiamine intake as estimated from a detailed diet history. Since no correlation between the fraction of the thiamine excreted and the habitual thiamine intake of the patient was found, it is concluded that this procedure is valueless for diagnosing subclinical thiamine deficiency.

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## GASTRIC EXCRETION OF NEUTRAL RED AS INFLUENCED BY VAGOTOMY

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### INTRODUCTION

If vagotomy as employed in the treatment of duodenal ulcer is to be defined as a procedure in which all the parasympathetic nerves to the stomach are interrupted, some method by which proof of this can be determined is necessary. Recent anatomic studies<sup>1, 2, 3</sup> have clearly demonstrated the many variations in pattern followed by the vagi, and it is unlikely that a surgeon can always be sure that all the fibers have been divided. Of the several methods employed, the one most nearly approaching the ideal of providing a vagal stimulus proximal to the point of section of the vagi, which would normally result in an ascertainable response in terms of gastric secretory or motor activity, is the insulin test, as observed by several investigators,<sup>4, 5, 6, 7, 8</sup> and further elaborated by Jemerin, Hollander, and Weinstein.<sup>9</sup> Comparison of several recent clinical reports<sup>10, 11, 12</sup> indicates, however, that there is lack of uniformity in the interpretation of the patterns of gastric secretory activity recorded during the test. Factors which tend to hinder accurate clinical interpretation of gastric response to pre- and post-operative insulin tests have been summarized by Hollander.<sup>12</sup> Considering these facts, a search for assistance in clarifying the status of patients in whom the post-operative insulin test was to any degree equivocal, seemed in order.

During examination of the various known aspects of the field of gastric physiology, our attention was drawn to the excretion of dyes as a gastric function which, while definitely separate from the secretion of acid, is yet related to it as being another specific activity of the parietal cell. The bulk of the previous work on excretion of dyes by the stomach has been concerned with neutral red, which was therefore selected as being the most suitable for further investigation of post-vagotomy changes in gastric function.

Neutral red\* is one of a group of basic dyes which possess certain distinctive physico-chemical characteristics which allow them to be excreted by the stomach. These have been described by Glaessner,<sup>14</sup> and Ingraham and Visscher.<sup>15</sup> Following the experimental observations of Fuld<sup>16</sup> and Finkelstein,<sup>17</sup> numerous investigators have employed neutral red in clinical investiga-

\* A pure preparation of the dye is not available at the present time. The dye used in this study was manufactured by the Allied Chemical and Dye Corporation, National Aniline Division, New York. It contains 73 per cent total dye content. The impurities in present supplies of neutral red consist of colorless dye intermediates.<sup>13</sup>

tions of normal and pathological gastric function.<sup>18, 19, 20, 21, 22, 23</sup> To Winkelstein<sup>24</sup> it appeared that "neutral red is a more delicate indicator of the functional activity of the gastric secretory cells than histamine." Gillman noted that "the excretion time of neutral red remains remarkably constant in the same individual on different occasions," in contrast to the fluctuations in acid secretion noted in the same subject at various times by Vanzant and Alvarez.<sup>25</sup> Gillman determined that after intravenous injection of the dye, patients without gastric disease excreted the dye into the stomach in less than nine minutes, averaging four minutes, and maximally concentrated the dye in six to twenty minutes, averaging fourteen minutes. Regarding patients with peptic ulcer Gillman concluded that (a) those with active ulcer usually show an accelerated neutral red "excretion time" of three minutes or less, (b) the maximal concentration of the dye in such cases is accelerated and more intense, (c) healed ulcers may exhibit a normal excretion time, and (d) an accelerated neutral red excretion time is a more constant finding in active peptic ulcer than is increased acidity.

The parietal cell has been shown to be the specific type of gastric secretory cell responsible for the excretion of neutral red.<sup>15, 19, 26, 27</sup> Recognition of the fact that neutral red excretion in the stomach is a specific function of the parietal cells would suggest that this process may be influenced by stimuli similar to those which cause alteration in their acid-secreting power. Glaessner<sup>14</sup> stated that insulin, histamine, and pilocarpine increased dye excretion, while atropine inhibited it. Tosaku was quoted by Speziale<sup>28</sup> as observing that after vagotomy in dogs, neutral red was not excreted. Kolm, Komarov and Shay<sup>29</sup> observed that the dye itself exerted a mild though definite secretagogue action on the gastric glands, increasing acidity more than peptic power. It appeared that neutral red possessed a physiologic action which affected the parietal cell through the vagal mechanism. From an examination of their published data it is evident that the quantitative excretion of neutral red itself was markedly diminished though not entirely abolished by the action of atropine. The exact effect on the excretion of neutral red, apart from its secretagogue action, of double cervical vagotomy done during the course of their experiments is not entirely clear. Further evidence of a central vagal stimulation was suggested by a slowing of the heart rate and a decrease in the amplitude of the pulse after injection of neutral red. These changes were not observed after double cervical vagotomy.

Consideration of the foregoing data would indicate that neutral red excretion would be diminished and retarded by bilateral vagotomy in man, and that such an effect might be sufficiently constant to indicate whether vagotomy had been complete, particularly if it appeared that partial vagotomy had little or no effect on the excretion time.

## METHOD

Simple gastric fistulas were created on each of twelve dogs. After complete recovery twenty-five to thirty milligrams of neutral red were injected intravenously into each animal, and the neutral red excretion time in the stomach was determined by the method to be described for the clinical cases. One dog was discarded for further use because of failure to excrete the dye within a normal time interval. The remaining eleven animals were subjected to trans-thoracic vagotomy, total in seven, and partial (seventy-five to ninety per cent) in four. Seven recovered normal health and vigor, and were thus available for comparative neutral red excretion studies before and after vagotomy. After completion of these investigations each animal was autopsied to determine whether the operative procedure had been carried out as planned.

TABLE 1

*Effect of Total and Partial Vagotomy on the Gastric Excretion of Neutral Red*

See text for reference to animal seven

ANIMAL NO.	POST-GASTROSTOMY NEUTRAL RED EXCRETION TIME	TYPE OF VAGUS SECTION	POST-VAGOTOMY NEUTRAL RED EXCRETION TIME
1	8 minutes	Total vagotomy	None in 30 minutes
3	5 minutes	Total vagotomy	None in 30 minutes
10	4 minutes	Total vagotomy	None in 30 minutes
7	10 minutes	Total vagotomy	21 minutes
4	2 minutes	Incomplete vagotomy	5 minutes
5	9 minutes	Incomplete vagotomy	7 minutes
9	4 minutes	Incomplete vagotomy	8 minutes

Examination of Table I indicates that partial vagotomy in which a given number of fibers were left intact had no significant effect on the excretion time of neutral red. Three of the four animals that presumably had a complete vagotomy failed to excrete neutral red within a thirty minute period. The fourth animal (No. 7) averaged a twenty-one minute dye excretion time after vagotomy. Autopsy examination of all animals except this one indicated that total vagotomy had been done where intended, and partial vagotomy had also been performed when planned. On examination of the left vagus in this animal a tenuous connection between the proximal and distal portions of the supposedly severed trunk appeared to remain, but the histologic evidence obtained was not regarded as conclusive proof of incomplete vagotomy.

Neutral red tests were also done on all animals immediately after closure of the chest and while still under anesthesia. In no animal was the dye recovered from the stomach in thirty minutes regardless of the type of vagotomy which had been done.

To confirm observation of others concerning other points of excretion of the dye, three acute experiments were done. The animals were prepared so specimens could be simultaneously and separately collected from the stomach, duodenum, pancreatic duct, hepatic ducts and ureter. In one animal on which a previous vagotomy had been done the dye was excreted from the liver and kidney only. In the other two unvagotomized animals dye was excreted from the stomach, liver and kidney. In no animal was dye excreted from the duodenum or pancreas.<sup>15, 30</sup> It was also noted that no dye could be recovered from a Thiry-Vella fistula on an otherwise normal dog during periods of observation up to two hours after intravenous administration of the dye. Excretion of the dye in the bile and failure of excretion in the small intestine in the dosages used in this investigation are points of practical importance in the clinical application of the test.

#### CLINICAL APPLICATION

A series of eighteen cases was studied in a clinical evaluation of the neutral red test, comparing dye excretion before and after vagotomy. The insulin test was used as an aid in the evaluation of the neutral red test in distinguishing complete from incomplete vagotomies. Thirteen of these were consecutive cases, and five were patients who were recalled for further study. Five had transthoracic operations and thirteen had transabdominal vagotomies. Three had had previous gastrojejunostomies elsewhere, and five had gastrojejunostomies performed concomitantly with vagotomy. Fifteen had duodenal ulcers and three had anastomotic ulcers at the site of the previous gastrojejunostomy.

The pre- and post-operative insulin tests were done as advised by Hollander with the following exceptions:

(1) The frequent necessity for repetition of the tests because of a failure of the blood sugar to drop to low enough levels, caused us to increase the intravenous insulin dosage from fifteen units as advised by Hollander<sup>12</sup> to twenty units. In a few cases repetition at this dosage was necessary and twenty-five units were employed. No case was accepted as demonstrating a negative insulin test unless the lowest blood sugar level during the procedure was less than 50 mg. per cent. Blood sugars were run immediately after being taken, employing the Folin-Wu method.

(2) Indicators used for determination of free and total acidity were Topfer's reagent for free acidity, and phenolphthalein for total acidity.

The neutral red solution was prepared by dissolving one gram of dye in 100 cc. of sterile water, the solution being heated to the boiling point for several minutes. The solution was then filtered through sterile gauze into a 100 cc. sterile vial and capped. This is essentially the method employed by Gillman.<sup>23</sup> The vials were autoclaved at fifteen pounds pressure for twenty minutes. One



preparation was made up as above and then passed through a Seitz-Werke filter into sterile containers. This preparation was not autoclaved. Cultures of the content of each vial were taken before it was used. These solutions were stored in a refrigerator for periods as long as three months before being used. The drug is apparently non-toxic in dosages used in this study.

Patients were prepared as for the insulin test. A Levine tube was introduced into the stomach and all fasting contents were withdrawn. If the contents were not clear, bile or other substances being present, gastric lavage was done with isotonic saline solution until clear. Five cubic centimeters of a one per cent solution of neutral red was then injected into an arm vein. Completion of the injection, which was carried out quite rapidly, was taken as the beginning of the time record. Specimens of gastric contents were then aspirated every half minute for the first five minutes and every minute thereafter. Specimens are difficult to obtain at such short intervals, therefore if one was not immediately forthcoming, 5-10 cc. of saline were injected into the Levine tube and withdrawn in a few seconds. The appearance of the first pink tinge to the aspirate was recorded as the excretion time. Aspirations were continued until the dye was maximally concentrated, although the exact time at which this occurred was not considered essential for the purposes of this study. If the dye failed to attain good concentration preoperatively, a rare occurrence in subjects with active ulcer, the test was repeated. Postoperatively the excretion time was again recorded, and aspirations were continued for thirty minutes if the dye failed to appear.

In this series the test was also employed at operation, dye being injected intravenously immediately after the surgeon signified that all vagal fibers had been severed. Use of the test at such a time will be discussed later.

The dye is red in water or saline, pink to crimson in low acid concentrations, and red or reddish violet in high acid concentrations. It is yellow to brownish-orange in alkaline solutions. If desired, dye standards varying from 1 to 20,000 to 1 to 300,000 in aqueous solution may be set up for comparison with the aspirate as suggested by Gillman.<sup>24</sup> This range will include concentrations of the dye usually excreted by the stomach.

Bile and blood may interfere with visualization of the excreted dye. Acidification of any specimen which appears to contain either of these, particularly all yellow or green specimens, will bring out the red color of the dye. Excess amounts of N/10 HCl or of glacial acetic acid may be used for this purpose. Acidification of a specimen which is red due to contained blood will result in a definite brownish color due to formation of acid hematin, and is easily distinguished from the pink to red color due to the dye. In the presence of a mixture of acid hematin and dye, filtering of the solution will leave the dye on the filter paper.<sup>19</sup> Bile, on the other hand, has been the source of more difficulty. If

the bile is not of sufficient amount and alkalinity (together with pancreatic and duodenal secretions) to change the acid reaction of the gastric juice to the alkaline side, the dye will still impart a red or orange color to the specimen. Although experience with the test enables one to detect the presence of the dye even in a mixture of bile and gastric secretion, all yellow specimens should be acidified, since the dye may be present in a yellow form. If any doubt is felt after acidification it is advisable to precipitate out the bile pigments so that the dye may be visualized in the supernatant fluid. Davidson's modification

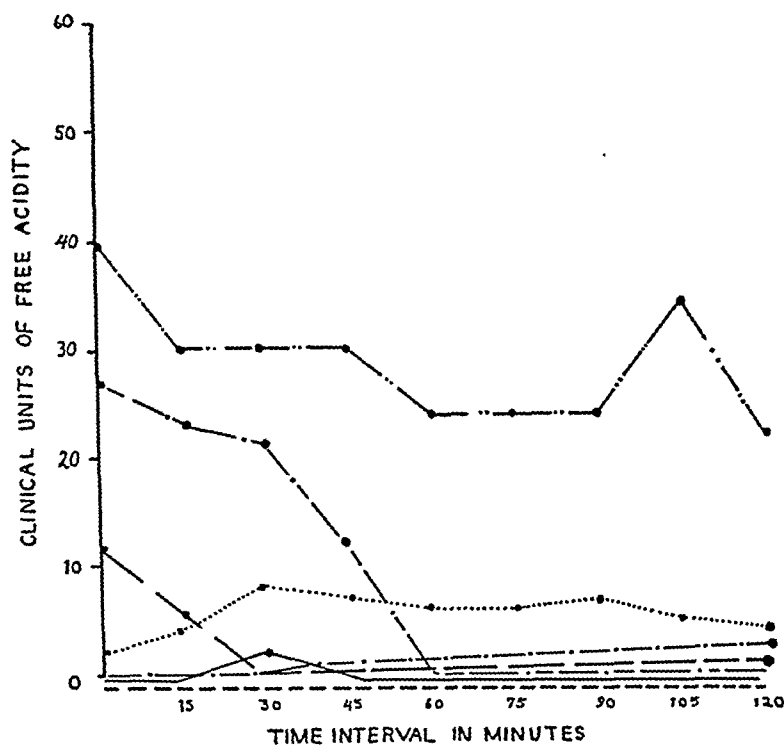


FIG. 1. Curves of free acidity in seven patients who had negative insulin tests and negative neutral red tests after vagotomy.

of Cowan's method\* has proved to be satisfactory the few times this was necessary.

Figures 1 and 2 illustrate the curves of free and total acidity in seven post-operative vagotomy cases which were negative to both the insulin and neutral red tests. Two additional cases which were negative to both tests demonstrated patterns of secretory response to insulin which were entirely similar to

\* Ten cubic centimeters of the specimen is placed in a centrifuge tube, and 0.3 cc. of a concentrated solution of lead acetate and 0.2 cc. of a concentrated solution of calcium chloride is added. This is heated in a water bath for five minutes, then centrifuged at high speed for ten minutes. The supernatant fluid can be inspected for the presence of the dye or compared with a standard aqueous solution.<sup>19</sup>

those illustrated. Frequent repetitions of the insulin test were necessary to insure correct classification of the type of secretory response. Eight cases showed positive response to both tests following vagotomy, indicating incomplete interruption of vagal fibers to the stomach. In seventeen cases, therefore, the two tests were in unequivocal agreement. The remaining case is of particular importance. A positive response to insulin could not be obtained preoperatively in this case, one of two in this series in which this occurred. The neutral red test showed an excretion time of one and one-half minutes preoperatively. Three insulin tests were performed at intervals of ten days, fifteen days and two months postoperatively. The lowest blood sugar levels reached

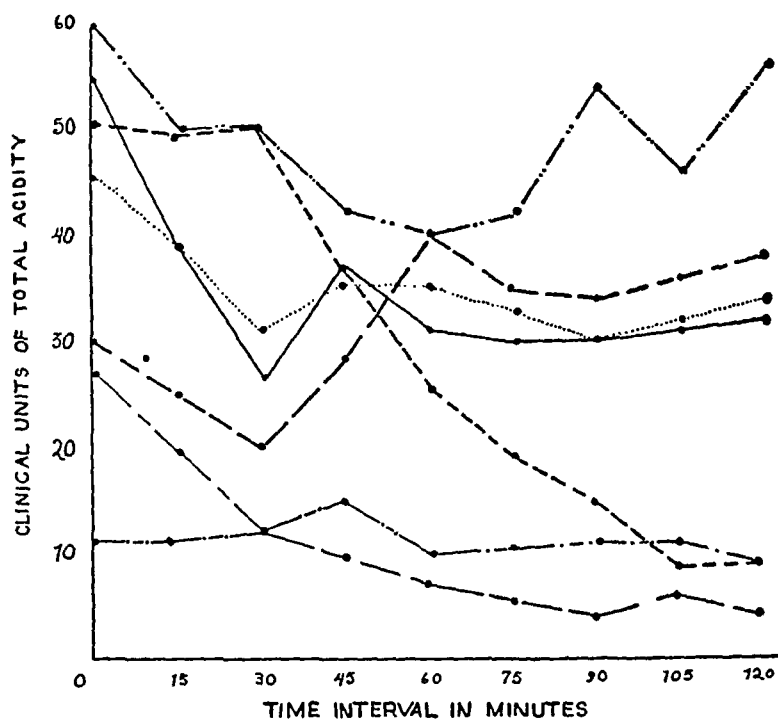


FIG. 2. Curves of total acidity in seven patients who had negative insulin tests and negative neutral red tests after vagotomy.

in these three tests varied from 46 mg. per cent in the first to 29 mg. per cent in the third. All tests were negative, and in the first two no free acid was obtained in any specimen. Specimens taken on two occasions without stimulation did show free acid, however. The neutral red test was positive on three occasions postoperatively, the excretion time varying from five to seven minutes. At the end of two months this patient still complained of epigastric distress, still presented mild epigastric tenderness to palpation, and roentgen examination demonstrated evidence of continued ulcer activity. In this patient, therefore, it seems apparent that the dye test more accurately determined the probable technical failure of the vagotomy.

## DISCUSSION

In this study the correct procedure and interpretation of the insulin test was of great importance, since it represented the best means of evaluating the possible constant nature of any other postvagotomy change in gastric function. Questions of procedure in the insulin test are predominately concerned with the degree of hypoglycemia which will coincide with a maximum stimulus to secretion of acid by the stomach. Jemerin, Hollander, and Weinstein<sup>9</sup> noted that usually the magnitude of the secretory response was roughly parallel to the

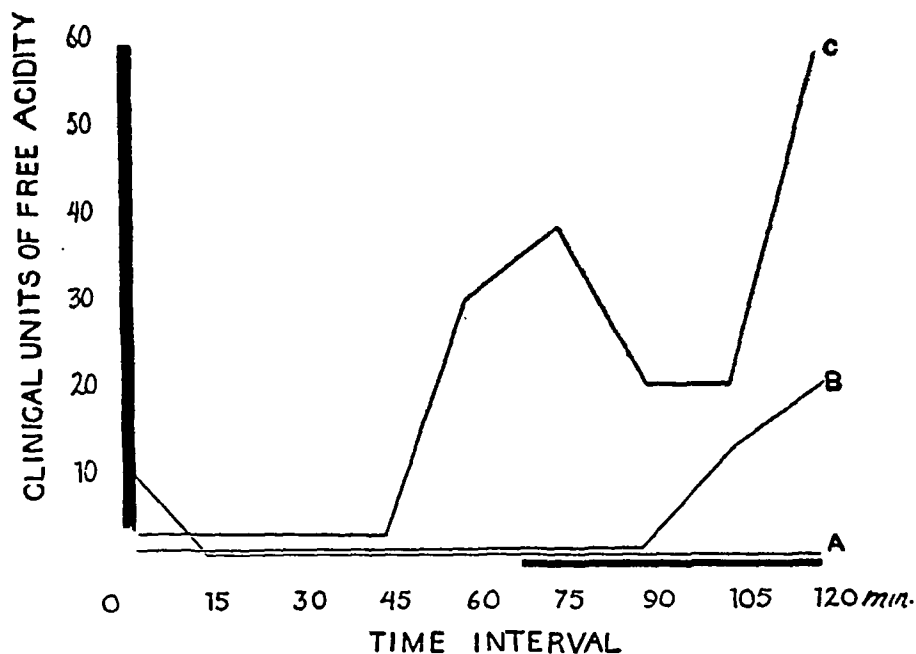


FIG. 3. Free acidity curves obtained in three consecutive insulin tests on the same patient, demonstrating increasing response to successively lower levels of blood sugar.

A—Minimum blood sugar during test—56 mg. per cent.

B—Minimum blood sugar during test—50 mg. per cent.

C—Minimum blood sugar during test—33 mg. per cent.

degree of hypoglycemia. However, Necheles and co-workers<sup>31, 32</sup> stated that production of too severe a degree of hypoglycemia resulted in depression of gastric motility and secretion.\* No evidence resulting from this study tends to confirm Necheles' results, although no attempt has been made to investigate these patients in relation to this still controversial point. An example of a patient who supports the original observation of Jemerin et al, is illustrated in Figure 3. In three insulin tests on this patient, no gastric secretory response

\* Necheles' results and a later observation of Hollander might indicate that the lower limit of hypoglycemia which would still result in an optimum stimulus would be about 30 mg. per cent. The minimum blood sugars during the insulin tests of the patients, whose acidity curves are illustrated in Figures 2 and 3 as constituting a negative response, varied from 24 mg. per cent to 44 mg. per cent. In all but two, at least one test was obtained in which the minimum was above 30 mg. per cent.

resulted from a minimum blood sugar of 56 mg. per cent, only a slight response from a second test in which the blood sugar fell to 50 mg. per cent, and a marked response in a third test, with a minimum blood sugar of 33 mg. per cent.

In the interpretation of the results of the insulin tests on these patients we have adhered to criteria similar to those indicated by Hollander.<sup>12</sup> Application of these criteria for a negative test has also resulted for us in high percentage of positive tests following operation. Although the usual indication for repetition of the test is failure to achieve a sufficiently low level of blood sugar, in our experience it has not infrequently been necessary to repeat the test to clarify the status of a patient from whom no free acid was obtained but whose values for total acidity were equivocal. Our evaluation of the reliability of the neutral red test obviously depends on the accuracy with which we have interpreted the insulin tests on this series of patients.

#### *Determination of a Negative Neutral Red Test*

The thirty minute period of observation necessary before a test was to be considered negative had to be arbitrarily selected. Glaessner<sup>14</sup> stated that after intramuscular injection, a period of sixty minutes in which no dye was excreted by the stomach could be considered as indicative of achlorhydria. This period could probably be shortened to thirty minutes after intravenous injection. Obviously, however, achlorhydria is not expected after vagotomy. That the time interval is approximately correct is indicated by the fact that in no positive postoperative case did the dye appear in the gastric aspirate in the interval between eighteen and thirty minutes after injection. In the majority of postoperative positives the dye will appear before ten minutes. It was noted by us, as it has been by others,<sup>14</sup> that the dye can be later excreted after longer intervals, either spontaneously, or in response to the first adequate stimulus to gastric secretion.

#### *Sources of Error in Neutral Red Test*

On one occasion a false negative was obtained postoperatively. In this case the first neutral red test was done on the fifth postoperative day and appeared to be negative. An insulin test done on the tenth day was equivocal. Subsequent insulin and neutral red tests were both positive. This error serves to emphasize the fact that temporary physiologic interruption of remaining intact nerve fibers does occur. No neutral red or insulin test has been accepted as negative unless it was performed at least ten days after operation, although it is quite desirable that results be confirmed at a later date by outpatient or office use of the neutral red test.

Previous objection to use of the dye in clinical practice has been largely concerned with the fact that it is excreted by the liver as well as the stomach, and

that the dye in bile might be regurgitated into the stomach. In our experience this has not been a source of error. It was determined on two patients with T-tubes in the common duct, whose liver function was within normal limits according to the usual tests, that the dye was excreted in bile very shortly after it appeared in the stomach. However, in order to result in a false appearance time in the stomach, bile from the liver must transverse the ampulla of Vater and regurgitate through the pylorus before excretion of the dye in the stomach occurred. This would never occur in ulcer cases preoperatively. Although the effect of vagotomy on the ampullary sphincter is perhaps not definitely predictable, there is good evidence to expect that passage of bile from the liver itself through the ampulla will be delayed after vagotomy.<sup>33</sup> Analysis of our postoperative positive cases, and comparison with the corresponding insulin tests, has convinced us that this error did not occur.

#### *Use of the Dye as an Operative Test*

Of great value to the surgeon performing a resection of the vagus nerves would be a simple procedure which would determine the operation to be incomplete while the operative field was still exposed. It seems probable that in some anatomically incomplete operations, the operative trauma may cause a physiologic interruption which will persist for a varying length of time.<sup>34</sup> The simplicity and innocuous nature of the dye test rendered it suitable for a trial during operation. Fifty milligrams of the dye were immediately injected intravenously when the surgeon signified that the nerves had been completely divided. In three instances the dye appeared in the gastric aspirate in less than thirty minutes, indicating that vagotomy was not complete. In one of these cases a twenty-eight minute wait was necessary. The incompleteness of the operations was later confirmed. However, in four cases which later were shown to be incomplete the dye did not appear while the patient was still on the table under anesthesia. Comparison of excretion times before and during anesthesia on patients undergoing operative procedures of other types indicates that anesthesia usually prolongs the excretion time. While the test will sometimes indicate cases of incomplete vagotomy while the patient is still on the operating table, it cannot be recommended for such use. It is also theoretically possible that, even in the presence of a complete vagotomy, the dye may be excreted from the stomach during the operation. This may be a result of (a) liberation of histamine due to the trauma of operation, and (b) temporary peripheral vagal stimulation as a result of manipulation incident to severing the nerves.

#### *Length of Time During Which the Test Will Remain Negative*

Since the clinical application of the test has been confined to a period of six months, there has thus far been insufficient opportunity to observe whether

the dye test will remain consistently negative for a long period of time. Similar doubts about the persistent negativity of the insulin test are only now beginning to be resolved. Three of the cases in this series had the dye test performed at a considerable interval after vagotomy; six, twelve and eighteen months, respectively. All three cases failed to excrete the dye and likewise had no response to insulin. Dye tests were not employed on these patients in the immediate postoperative period, but it may be reasonably presumed that they would have been negative.

### *Size of the Neutral Red Test Dose*

In the majority of these cases fifty milligrams (5 cc. of a 1 per cent solution) was employed as the test dose. It is probable that the size of the dose may have some influence on the excretion of the dye by the stomach, though the exact importance of this factor is not known to us. Glaessner is of the opinion that the drug should be administered intramuscularly, but in Gillman's experience the intravenous administration proved to be satisfactory. It was noted on one ulcer patient that a five milligram dose was quickly excreted by the stomach, although concentration of this amount was not as marked as the fifty milligram dose. Investigation at this hospital, independent of this study,<sup>35</sup> indicates that in normal patients the drug begins to appear in the gastric aspirate when the concentration is near 1.4 gamma per cc. of blood. It appears that less than ten milligrams would then be sufficient. Following these observations, forty milligrams have been employed and found to be satisfactory.

### *Simultaneous Use of Neutral Red and Insulin*

In three cases neutral red was injected during the height of the hypoglycemic reaction of the insulin test. All three cases were negative to both neutral red and insulin administered separately. When given together as described, no dye was excreted by two, but a faint trace appeared at eight minutes in the third without increase in concentration. Investigation concerning the simultaneous use of the insulin and neutral red tests were not followed further since a separate evaluation of neutral red was more desirable.

### *Advantages of Neutral Red*

Administration of the dye is innocuous and without unpleasant reaction for the patient. Visualization of the first appearance of the dye is extremely easy except when regurgitation occurs and even then is not difficult after brief experience. In the use of the insulin test it must be remembered that it is possible that regurgitation from the duodenum, or jejunum (in cases with gastroenterostomy) may neutralize small amounts of acid that are secreted. A tem-

porary depression of gastric secretory activity may also be present. Neither of these factors should be a source of error when using the dye. It has not seemed necessary to complicate the procedure by quantitative determinations. Performance of the test is not time consuming and can be performed in the office or out-patient clinic. The patient should be advised that the dye will appear in the urine.

### *Reliability in Evaluation of Complete Vagotomy*

While in this series of cases the dye has appeared to be as reliable as the insulin test, it is not advised that it be employed as a substitute. It is better designated as an important supplemental means of evaluation. Unlike the insulin test, a preliminary theoretical prediction that the excretion of neutral red would invariably be retarded after vagotomy could not be made, since the pharmacology of the dye is not well known. Results of the clinical experience with the dye as reported in this paper clearly establish its value as an aid in the postoperative study of patients who have undergone vagotomy, and it is expected that further clinical and experimental investigations being carried out at this hospital on patients subjected to vagotomy, or high gastric resection with or without vagotomy, will continue to substantiate this opinion.

### CONCLUSIONS AND SUMMARY

Previous clinical and experimental experience with the use of neutral red in the study of gastric function has been briefly reviewed. Additional investigation of the excretion of this dye by the stomach following intravenous injection of forty to fifty milligrams of a one per cent solution before and after bilateral interruption of vagus fibers to the stomach has resulted in the following conclusions:

- (1) Incomplete vagotomy does not retard the gastric excretion of neutral red to a constant or significant degree.
- (2) Complete bilateral vagotomy markedly delays the gastric excretion of neutral red provided no other stimuli to gastric secretory activity are acting.
- (3) Observations on a small series of patients subjected to vagotomy for peptic ulcer, and subsequently evaluated by both insulin and neutral red tests, indicate that neutral red is of great assistance in segregating cases in which vagotomy was complete from those in which it was incomplete.
- (4) Combined use of the insulin and neutral red tests may increase the percentage of vagotomies that will be considered incomplete.

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## HORMONAL AND VITAMIN FACTORS IN INTESTINAL ABSORPTION\*

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### INTRODUCTION

In a discussion of metabolic functions of hormones Dempsey<sup>1</sup> tentatively suggested the possibility that an altered endocrine balance may express its effects through modifications in the equilibrium between competing enzyme systems. Certain vitamins in combination with proteins are known to form enzyme systems in the intestinal mucosa which are essential for the performance of work required for the transport across the mucosal barrier of food substances absorbed at rates greater than their normal rates of diffusion. Certain hormones serve directly or indirectly as regulators for these enzyme systems. The experimental work related below was undertaken in order to clarify the part played by some of the hormonal and vitamin factors concerned in intestinal absorption with the object of applying this knowledge to clinical problems.

### EXPERIMENTAL METHODS

Our data, except those dealing with renal tubular reabsorption were obtained from experiments on female rats aged between 5 and 7 months, which came from the colony of the University of California Institute of Experimental Biology. During experiments these rats were kept in a room thermostatically controlled at  $27 \pm 1^\circ\text{C}$ . In order to produce a hormonal deficiency in our rats, various endocrine organs were excised under ether anesthesia. Rats were rendered hyperthyroid by intraperitoneal injections of 0.1 mgm. of thyroxin per 100 gm. of weight, given daily for 12 days. For the nutrition experiments the rats were kept on a synthetic diet deficient in vitamin B complex. To induce recovery a vitamin supplement adequate in the various B factors was added.<sup>2</sup> For determinations of the rate of intestinal absorption the rats were fasted for 24 hours in a metabolic cage to clear their intestines and were then given by stomach tube known amounts of various substances. After a specified length of time the rats were sacrificed, the residue in the digestive tract was determined, and the amount absorbed per 100 gm. of weight was calculated. The BMR was determined by the use of a closed circuit apparatus described by Schwabe and Griffith.<sup>3</sup> The experimental data on rats recovering from a vitamin B complex deficiency were obtained after the individual rats

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had regained their original weight. The oxygen consumption of intestinal tissue slices was measured in a standard Warburg apparatus.

Data on the maximum rates of transfer of glucose and of diodrast by the renal tubules were obtained from female dogs by the method of Shannon and Fisher<sup>4</sup> before and after they were rendered hyperthyroid by subcutaneous injections of 20 to 45 mgm. of thyroxin daily for at least 5 days.

The data obtained in each series of experiments were evaluated statistically and are presented in the accompanying diagrams in percentages of the mean normal values.

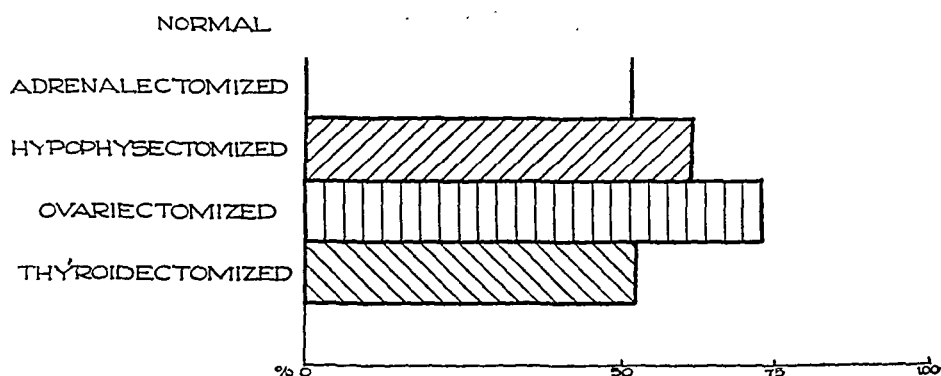


FIG. 1. Intestinal absorption of glucose in (female) rats after removal of various endocrine organs

## RESULTS AND DISCUSSION

### *Hormones*

Removal of the adrenals, hypophysis, ovaries, or thyroid gland is followed by a decrease in intestinal absorption of glucose<sup>5</sup> (Fig. 1). Ablation of the testes has no such effect.

The hormones of the adrenal cortex, anterior lobe of the hypophysis, and ovaries exert their influence on intestinal absorption indirectly. This is shown by observations of several investigators, including our own, that administration of these hormones in excess to normal animals does not accelerate intestinal absorption. There is also other experimental evidence to this effect. We were able to show that adrenalectomized rats recover normal intestinal absorption when fed sodium chloride.<sup>6</sup> Hypophysectomized rats do not respond with increased intestinal absorption to injections of anterior pituitary extracts over periods sufficient to correct other anomalies of their carbohydrate metabolism but do respond to injections of minute amounts (10 $\gamma$ ) of thyroxin.<sup>7</sup> This indicates that the hypophysis affects intestinal absorption through the action of its thyreotropic hormone on the thyroid gland. Finally we demonstrated that removal of the ovaries decreases intestinal absorption only if carried out in very young animals.<sup>8</sup>

The thyroid hormone when administered to normal rats in doses sufficient to increase the BMR by 50 per cent, produces a marked increase in intestinal absorption of glucose above the normal rate. Experimental hyperthyroidism also increases the intestinal absorption of galactose, starch, and oleic acid (Fig. 2). These substances have in common two characteristics: They enjoy preferential intestinal absorption which requires metabolic work, and they are susceptible to obligate (direct) phosphorylation. Administration of thyroid hormone does not increase the intestinal absorption of xylose, alanin, or calcium lactate (Fig. 2)—substances which are absorbed by simple diffusion and which are incapable of obligate phosphorylation.

These experiments indicate that the thyroid hormone influences absorption not by increasing the permeability of the intestinal mucosa in general, but by

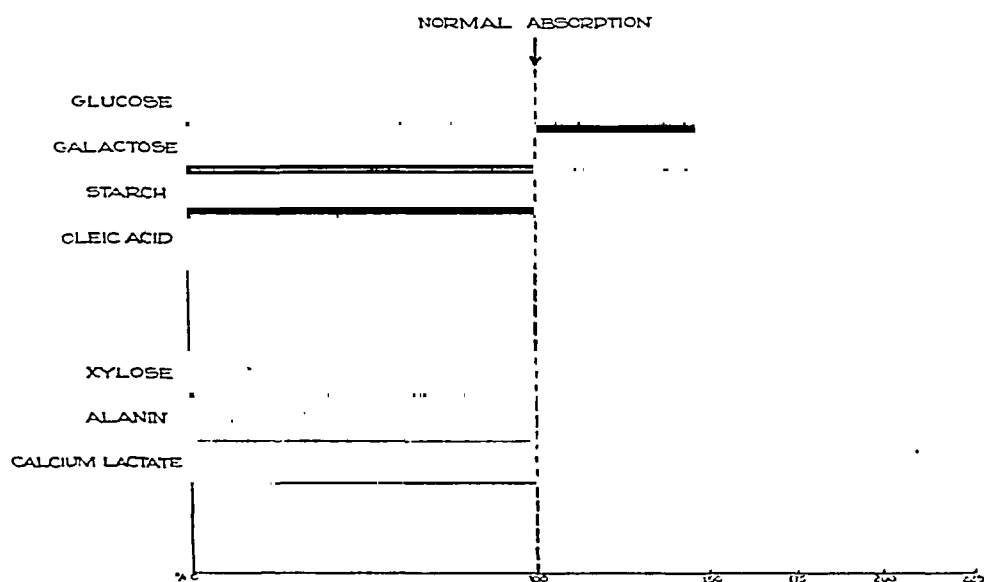


FIG. 2. Intestinal absorption of various food elements in hyperthyroid rats.

stimulating the chemical mechanism which is responsible for preferential absorption. According to the hypothesis advanced by Wilbrand and Laszt<sup>9</sup> and adopted by many investigators, preferential absorption of glucose is accomplished through obligate phosphorylation or conversion of each molecule of glucose to a hexosephosphate as soon as it enters a mucosal cell. In this manner the concentration of glucose within the cells of the mucosa is kept very low and a steep diffusion gradient is maintained across the mucosal cell barrier proximal to the intestinal lumen. To complete the process of absorption, hydrolysis of the hexosephosphate with liberation of a molecule of glucose must occur at the mucosal cell barrier distal to the intestinal lumen before the glucose can reach the circulation.

To investigate the bearing of this hypothesis on the stimulating action of

thyroid hormone on preferential intestinal absorption phlorizin, which inhibits phosphorylation, was used in absorption experiments with three key substances. As seen from Figure 3, the addition of phlorizin to the solution of glucose reduced its rate of intestinal absorption in normal rats to the rate of absorption of xylose which is absorbed by simple diffusion. This indicates that the entire mechanism of preferential absorption of glucose was paralyzed. Since the presence of phlorizin also reduced the absorption of glucose in hyperthyroid rats to the same level, the conclusion is justified that the acceleration of intestinal absorption of glucose by the thyroid hormone is effected through

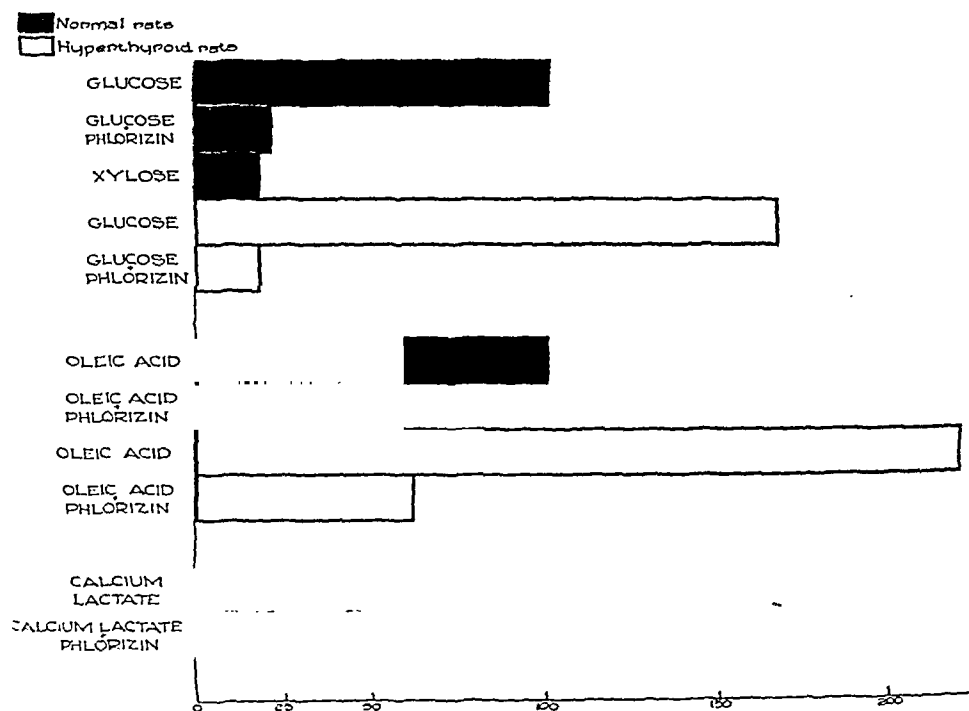


FIG. 3. Influence of phlorizin on intestinal absorption of rats.

stimulation of phosphorylation in the mucosa. This conclusion is supported by our observation that phlorizin also decreased the absorption of oleic acid and that the decrease was to the same level in normal and in hyperthyroid rats. The possibility that phlorizin may decrease intestinal absorption in general was ruled out by showing that it did not affect the absorption of calcium lactate which is absorbed by simple diffusion.

In an effort to obtain further proof for the mechanism of preferential intestinal absorption by obligate phosphorylation, we studied the concentration of different fractions of acid soluble phosphate in the intestinal mucosa during absorption of glucose in normal, in hyperthyroid, and in thyroidectomized

rats, and compared it to that observed during absorption of sodium chloride.<sup>10</sup> Our results showed a 15 per cent increase in the acid soluble phosphate esters during absorption of glucose but the rate of absorption of glucose as determined by the difference in thyroid status had no significant effect on the concentration of these esters. A positive correlation would have supported the hypothesis that obligate phosphorylation is concerned with preferential intestinal absorption of glucose. A lack of correlation does not necessarily militate against it because a more rapid turnover of the acid soluble phosphate esters would accomplish the same purpose as an increase in concentration.

Separate experiments ruled out as important factors accounting for the effect of thyroid hormone on preferential intestinal absorption: A rise in body temperature, an increase in basal metabolism per se (as produced by administration of dinitrophenol and as seen in human leukemia), a rise in the velocity of the blood flow, acceleration of gastric emptying, and stimulation of intestinal peristalsis.<sup>11</sup> In order to make our findings more decisive, we took advantage of the similarity between the intestinal absorption of glucose and the resorption of glucose from the glomerular filtrate by the renal tubules. In both instances the absorption involves a selective and active transfer of glucose across an epithelial barrier at a rate which, within wide limits, is independent of concentration. A further similarity between these two organs is that phlorizin decreases the rate of absorption for glucose in both. By studying the influence of the thyroid hormone on tubular resorption of glucose in normal and in hyperthyroid dogs, it was hoped to rule out the indirect influence of this hormone on any physiological mechanism which the intestine and the kidneys do not share.<sup>12</sup> From Figure 4 it is seen that administration of thyroxin increased the rate of resorption of glucose in the renal tubules of dogs approximately to the same degree as the rate of intestinal absorption of this sugar in rats. In another experiment, we studied the effect of thyroid hormone on the tubular resorption of galactose.<sup>13</sup> The transfer mechanism for galactose in the renal tubules unlike that in the intestine is limited, probably by the presence of only small amounts of galactose-hexokinase in the kidneys. As seen in Figure 4, administration of thyroid hormone failed to increase the tubular resorption of galactose indicating that in the kidneys similarly to the intestine, there is no general increase in absorption connected with the hyperthyroid state. These two experiments furnished additional evidence in favor of a specific effect of the thyroid hormone on the mechanism of preferential absorption both in the intestine and in the kidneys.

In order to obtain more information on the mechanism by which the thyroid hormone affects tubular resorption of glucose, we studied its effects on the excretion of diodrast. Diodrast resembles glucose in that it has a maximum rate of tubular transfer in the kidneys which requires metabolic work. On the

other hand, the renal transfer of diodrast does not involve obligate phosphorylation as was postulated by Wilbrandt and Laszt to explain the preferential intestinal absorption of glucose and of other substances susceptible to obligate phosphorylation. In Figure 4 it is seen that the excretion of diodrast in the renal tubules of the hyperthyroid dogs was increased even more than the re-sorption of glucose. From this finding and from the fact that phlorizin inhibits the tubular transfer of diodrast as well as of glucose, it is permissible to postulate that while the possibility of obligate phosphorylation in some phase of intestinal absorption of glucose is not excluded, the emphasis should be shifted from obligate phosphorylation with incidental liberation of energy to a

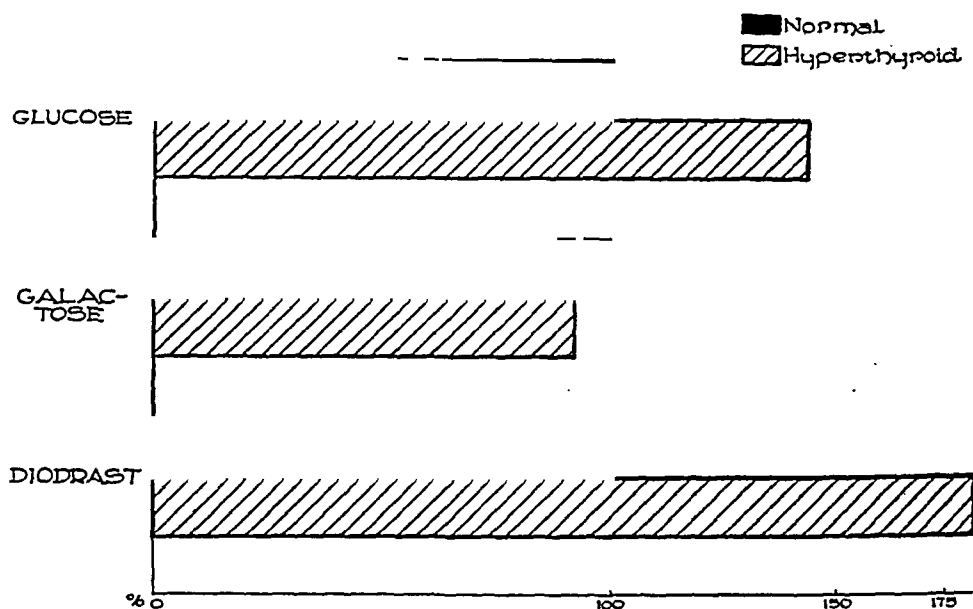


FIG. 4. Effect of the thyroid hormone on the maximum rate of transfer ( $TM$ ) of glucose and diodrast, and on absorption of galactose by the renal tubes of dogs.

primary role of phosphorylation as a transmitter of oxidative energy required for all types of preferential absorption whether involving obligate phosphorylation or not.

In a prior publication<sup>12</sup> we proposed that the thyroid hormone influences the concentration or activity of one of the factors involved in the transfer of phosphate bond energy. Since the work of several investigators indicates that adenosine-triphosphatase probably acts as a catalyst in the transfer of phosphate bond energy, we suggested that the thyroid hormone could account for an increase in the rate of transfer of energy by changing the concentration or activity of this enzyme.

### Vitamins

Several components of the vitamin B complex enter prominently into the formation of enzymes. Thiamine, riboflavin, pyridoxine, pantothenic acid, nicotinamide, and biotin are known to act as co-enzymes or to form prosthetic (active) groups in several enzymes which play an essential part in oxidative phosphorylation.<sup>14</sup> The latter as discussed above, acts as a transmitter of energy which is necessary for preferential intestinal absorption of certain food-stuffs. For these reasons, we undertook to study the influence of the vitamin B complex on intestinal absorption.

As seen from Figure 5, dietary deficiency of the vitamin B complex leads to a pronounced decrease in intestinal absorption of glucose. The decrease in absorption becomes more marked as the rats are kept longer on a B deficient diet. On the other hand, intestinal absorption of xylose in these rats was unchanged. These experiments can be taken as proof that vitamin B complex plays an im-

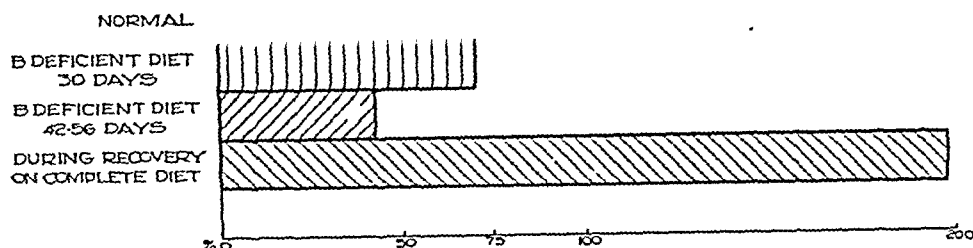


FIG. 5. Intestinal absorption of glucose in rats on a vitamin B deficient diet and during recovery on a vitamin B supplement.

portant part in preferential intestinal absorption, but not in absorption by simple diffusion. It is true that the lack of vitamin B complex and especially of thiamine interferes with the appetite of the animals and leads to severe caloric under-nutrition. On the other hand, we showed in some previous work<sup>11</sup> that even total starvation causes only a moderate (15 per cent) decrease in intestinal absorption of glucose and that the maximum decrease is reached after two days' fasting with no further diminution in absorption at the end of three or four days.

An excess of vitamin B complex in normal animals, unlike that of a regulatory hormone (e.g. the thyroid hormone) would not be expected to increase preferential intestinal absorption because the enzyme systems, of which various B vitamins are important constituents, are already present in abundance and therefore do not act as a limiting factor in the chain of enzymatic reactions. Absorption experiments on rats which received large doses of vitamin B complex bore out this reasoning. Therefore, if the importance of the B vitamins



for preferential intestinal absorption was to be demonstrated in a positive way, a different experimental approach became necessary. The approach adopted by us was to render rats deficient in vitamin B complex and to study their intestinal absorption while the rats were recovering on an adequate vitamin B supplement. From Figure 5 it is seen that our recovering rats absorbed glucose at a greatly increased rate which exceeded even that observed in our hyperthyroid animals.

Since the rats recovering from vitamin B deficiency showed an extremely rapid gain in weight (at  $7\frac{1}{2}$  times the normal rate) the question arose whether the increase in preferential intestinal absorption might not be due to a general rise in metabolism incident to the rapid growth of tissues. As a check on this possibility, and also in order to learn the effects of vitamin B deficiency on metabolism in general, the BMR of B deficient and of recovering rats was studied. These studies revealed that the BMR of vitamin B deficient rats was considerably lower than normal (Fig. 6). This is probably due not ex-

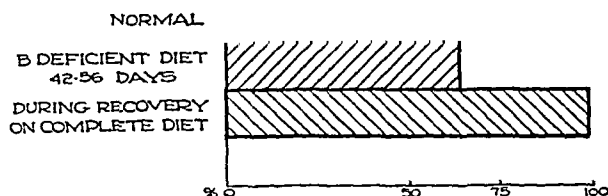


FIG. 6. B.M.R. of rats on a vitamin B deficient diet and during recovery on a vitamin B supplement.

clusively to a specific effect of vitamin B deficiency on the enzyme systems involved in biological oxidation, but is caused at least in part by caloric undernutrition. The high RQ in our B deficient rats favors this interpretation. During recovery from B deficiency the BMR of our rats was shown to have returned to normal but was not abnormally high. This outcome of the BMR determination rules out a general increase in metabolism as an explanation for the greatly increased intestinal absorption of glucose during recovery. It thus lends support to the concept that vitamin B complex plays a specific part in preferential intestinal absorption through participation in the oxidative enzyme systems of the intestinal mucosa.

With the object of learning more about the influence of vitamin B complex on the local energy production in the intestine, we compared in the Warburg apparatus the oxygen consumption of intestinal tissue slices from B deficient rats and from rats recovering on a vitamin B supplement with that of normal and of hyperthyroid rats.<sup>15</sup> As seen in Figure 7, there was a marked reduction in local oxygen consumption and consequently in energy production in the intestine of B deficient rats. This reduction was proportional to the decrease

in intestinal absorption of glucose in these rats. Rats recovering on a vitamin B supplement showed a moderate but statistically highly significant increase in local oxygen consumption which corresponds to a marked rise in intestinal absorption of glucose. These findings show that variations in preferential intestinal absorption of glucose as determined by the vitamin B status of animals go hand in hand with variations in the local production of energy. Our conclusion from this is that vitamin B complex specifically influences preferential intestinal absorption through the enzyme systems involved in the liberation of energy in the cells of the mucosa. Hyperthyroid rats were also found to

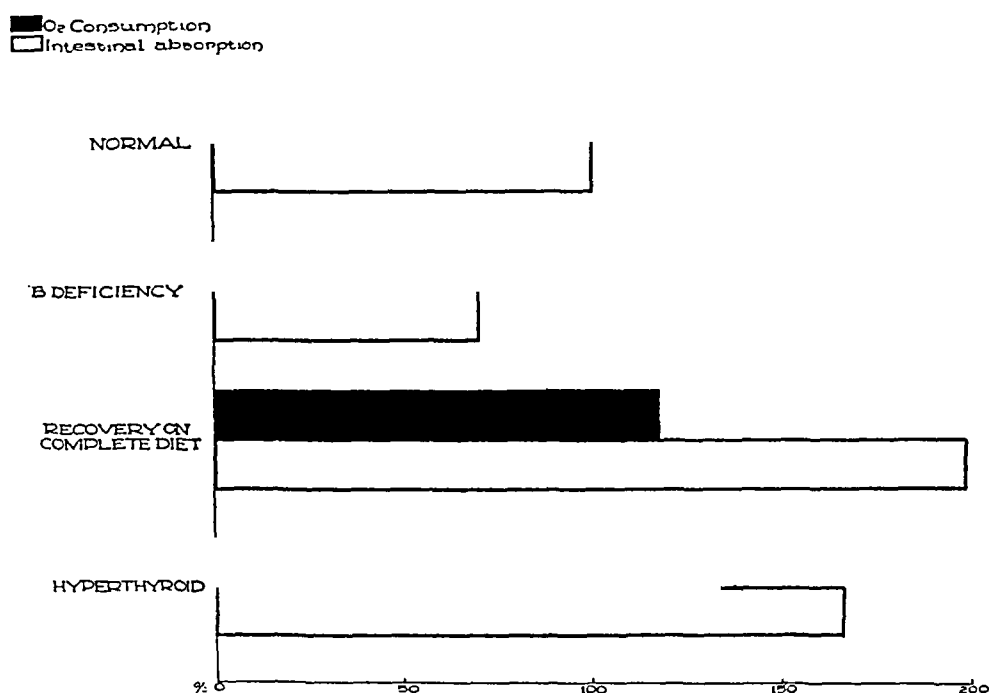


FIG. 7. Oxygen consumption of tissue slices of the intestine and intestinal absorption as influenced by vitamin B and by the thyroid hormone.

have a considerable increase in local oxygen consumption corresponding to their increase in the rate of intestinal absorption of glucose. This finding supports our suggestion that the thyroid hormone influences preferential absorption in the intestine through activation of the oxidative enzyme systems.

#### CLINICAL APPLICATIONS

##### *Hyperthyroidism*

The most fruitful clinical application of this work took place in the field of disorders of the thyroid gland. It is possible to obtain an estimate of the rate of preferential intestinal absorption in man by administering 40 grams of

galactose by mouth and making determinations of galactose in the blood at suitable intervals.<sup>16</sup> By this method it was found that patients suffering from hyperthyroidism had considerably higher oral galactose tolerance curves than normal persons or patients suffering from other diseases except Paget's disease or diseases of the liver (Fig. 8). Significant participation of hepatic insufficiency\* in the high galactose curves of patients with hyperthyroidism was ruled out by an intravenous galactose tolerance test performed in 10 of our patients who had the highest galactose values in the blood following oral administration of this sugar.<sup>17</sup> This was also confirmed by a prompt lowering of the oral galactose tolerance curves in our hyperthyroid patients after thyroidectomy. The oral galactose test proved to be of value in the differential diagnosis of

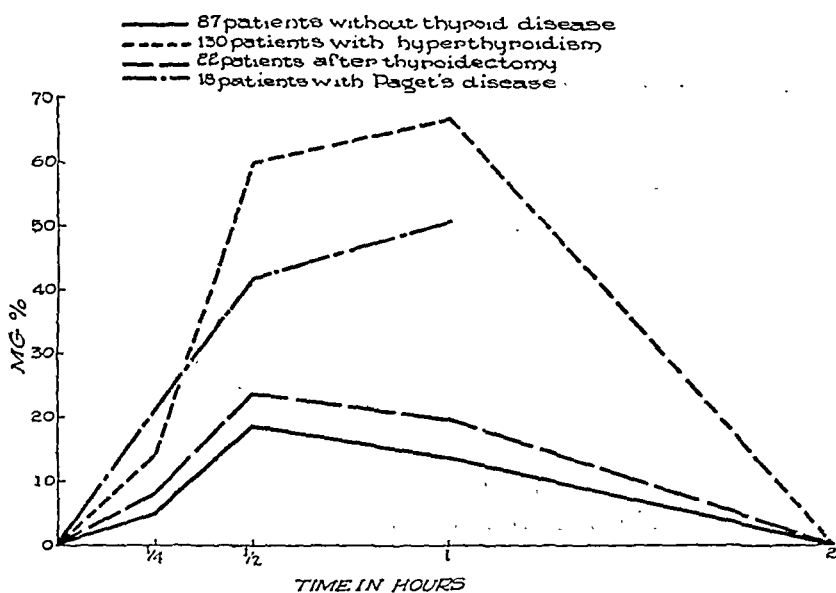


FIG. 8. Oral galactose tolerance test.

hyperthyroidism especially in cases where the BMR is in the borderline zone, or where hyperventilation due to anxiety or to cardiac disease interferes with satisfactory determinations of the BMR.

Our work also furnished certain therapeutic principles applicable to hyperthyroidism.<sup>18</sup> Glycosuria, postprandial hyperglycemia and high oral glucose tolerance curves can be found in approximately one-half of patients with hyperthyroidism and when discovered, are often thought to indicate a diabetic "anlage" or frank diabetes mellitus and are treated accordingly. Actually, these phenomena are due to an accelerated intestinal absorption of sugars and starches and have no disquieting significance unless the fasting blood sugar

\* Hepatic insufficiency is known to reduce the ability of the liver to metabolize galactose and its presence invalidates the significance of the oral galactose tolerance test.

is also high. However, another less innocuous disturbance of carbohydrate metabolism in hyperthyroidism is an increased rate of oxidation of glucose in the tissues leading to a depletion of glycogen stores especially in the liver. From the viewpoint of this disturbance the usual remedies for diabetes, namely dietary limitation of carbohydrates and administration of insulin, are detrimental to the patient with hyperthyroidism when they are prescribed on the mistaken assumption that diabetes is also present, because they lead to a further depletion of hepatic glycogen. The logical diet for such a patient is one high in calories and starches. Furthermore insulin should be withheld in such cases even when glycosuria, postprandial hyperglycemia and a high oral glucose tolerance curve are present as long as the fasting blood sugar level is not elevated.

### *Myxedema*

Analogous to our experimental data showing reduced intestinal absorption of glucose in thyroidectomized rats, patients with myxedema have very low oral galactose tolerance curves. Reduced intestinal absorption offers a good explanation for the well known low oral glucose tolerance curves in such patients. Heretofore these usually had been ascribed to greater than normal utilization of glucose. Administration of thyroid substance corrects this anomaly of intestinal absorption more rapidly than it raises the BMR.<sup>7</sup>

### *Paget's disease*

Many patients with Paget's disease are found to have glycosuria, postprandial hyperglycemia, or high oral glucose tolerance curves and disturbances of various endocrine organs have been postulated to explain these findings. The high oral galactose tolerance curves observed in most of our patients with Paget's disease (Fig. 8) indicate that, as in the case of hyperthyroidism, these phenomena are due to increased preferential intestinal absorption and not to diabetes mellitus, except when a high fasting blood sugar level is also present. Reduced capacity to metabolize galactose was ruled out by a normal intravenous galactose test in several patients. The reason for the increased preferential intestinal absorption is obscure. It does not appear to be correlated either with the BMR, or with the level of alkaline phosphatase in the serum.<sup>19</sup>

### *Adrenal Disease*

In hypoadrenalism of Addison's disease, galactose was found to be absorbed from the intestine at an abnormally low rate. On the other hand, patients with hyperadrenalism of Cushing's syndrome did not have abnormally rapid absorption of this sugar.<sup>20</sup> In both respects our experimental work with rats was confirmed.

*Pellagra*

In a single case of typical pellagra the intestinal absorption of galactose was markedly reduced. Three weeks after the beginning of successful treatment with nicotinic acid and brewer's yeast the oral galactose tolerance curve was higher than in any of our normal controls and the peak of the curve was twice as high as the peak of the average normal curve. These changes in intestinal absorption are analogous to the changes seen in our rats on the vitamin B complex deficient diet and during recovery on the vitamin B supplement.

*A New Clinical Concept*

In conclusion it may be pointed out that one result of our work on absorption has been the introduction of the concept of abnormally increased intestinal absorption into clinical medicine. Heretofore abnormalities of absorption in the intestine have been associated only with a decrease in absorption and the resulting general or specific undernutrition. In the future the possibility of pathologically accelerated intestinal absorption leading to a flooding of the blood stream with certain substances and possibly an over-loading of organs concerned with assimilation of these substances will have to be taken into consideration as exemplified by hyperthyroidism and by Paget's disease. For instance, the increased incidence of true diabetes mellitus in patients with hyperthyroidism which was pointed out by John<sup>21</sup> may be due to accelerated intestinal absorption of carbohydrates.

## SUMMARY AND CONCLUSIONS

The presence of several endocrine glands is necessary for optimum intestinal absorption of substances which enjoy preferential absorption in the intestine. Hormones of the adrenal cortex, of the hypophysis, and of the ovaries exert their influence on intestinal absorption indirectly. The thyroid hormone has a direct stimulating effect on the preferential intestinal absorption of substances susceptible to obligate phosphorylation (e.g. carbohydrates and fats). This stimulating effect of the thyroid hormone is mediated through phosphorylation. In the renal tubules the thyroid hormone stimulates selective resorption of glucose which is susceptible to obligate phosphorylation, and selective excretion of diodrast which is incapable of obligate phosphorylation. These effects of the thyroid hormone can be explained by the assumption that phosphorylation brings about preferential absorption mainly by acting as a transmitter of oxidative energy rather than by obligate phosphorylation.

Vitamin B complex which through several of its components enters into the formation of enzymes that play an essential part in phosphorylation, is indispensable for normal absorption of glucose in the intestine. During re-

covery from vitamin B deficiency, a marked increase above normal in intestinal absorption of glucose takes place, supporting the concept that vitamin B complex plays a specific part in preferential intestinal absorption. Studies of oxygen consumption by intestinal tissue slices in normal, B deficient, recovering, and hyperthyroid rats, show a positive correlation between local production of oxidative energy and preferential intestinal absorption. For these reasons it is suggested that the thyroid hormone controls preferential absorption in the intestine through activation of the oxidative enzyme systems in which several B vitamins play a dominant part.

On the clinical side it was possible to confirm the experimental results with oral galactose tolerance curves in patients with hyperthyroidism, with myxedema, with Addison's disease, with Cushing's syndrome, and in one case of pellagra. In addition, the anomalies of carbohydrate metabolism characteristic of myxedema, of hyperthyroidism and of Paget's disease were satisfactorily explained on the basis of disturbed intestinal absorption. Thus in the two latter diseases the presence of a tendency to diabetes mellitus was ruled out except as an infrequent complication in prolonged cases. Oral galactose tolerance curves were shown to be useful in the differential diagnosis of doubtful cases of hyperthyroidism, except in the presence of hepatic insufficiency. Finally a new clinical concept of abnormally rapid intestinal absorption was established.

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# Case Reports

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## HEPATOGENOUS JAUNDICE IN A CASE OF MALARIA

### SECONDARY OR COEXISTENT?\*

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### INTRODUCTION

Hemolytic jaundice in the course of malaria is a common and well understood phenomenon. Hepatogenous jaundice, on the contrary, is very unusual. Consequently, the association of an hepatogenous jaundice with the malarial infection, always causes doubt. The existence of this rare association in one of our patients, explains this paper with the interrogative sub-title.

Furthermore, the fact that we were able to follow the course of the liver process very closely, through serial biopsies and repeated functional tests, and the scarce publications dealing with biopsy studies of the malarial liver in the living, makes us believe this case worthy of report.

### PRESENTATION OF THE CASE

*History.* The patient, a 22 year old white male, was admitted to the Calixto Garcia University Hospital on February 13th, 1948. Family history and habits were non-contributory. Past history, revealed a questionable malarial attack, when the patient was only five years old, which lasted only a few days. He dated his present illness from November 25th, 1947, at which time, he had paroxysms of fever, with temperatures up to 40°C. (axilla), accompanied by chills. Temperature elevation came suddenly about 6 p.m. every day lasting for three hours. Anorexia, belching, vomiting and a mild diarrhea were also present. This clinical picture lasted ten days after which the patient returned to a normal condition. A few days afterwards, the patient noticed a yellowish discoloration of his skin, which increased progressively, observing also that the urine was dark in color and the stools were light colored. The patient said that his symptoms had decreased lately, while the urine still was dark. After an absence of fever since December 5th (2½ months), the patient complains once more of new paroxysms of fever, accompanied by chills, reappearing three for four days before his admission to the hospital.

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*Physical Examination.* Fair general aspect, with a moderate jaundice, mixed to a lemon discoloration of the skin. Temperature 38°C. Tachycardia. Enlarged liver with upper border of liver dullness at the fifth rib. In the mid-clavicular line, and on deep inspiration, the lowermost portion of the liver could be felt four fingerbreadths below the costal margin. The liver was somewhat painful and firm in the epigastrium. An enlarged spleen could also be felt five fingerbreadths below the costal margin, firm and very painful. The remainder of the physical examination was negative.

#### PROVISIONAL DIAGNOSIS

Malaria.

Hepatogenous jaundice: Secondary to malaria or coexistent?

The development, in a young man, coming from a possible malarial region (San Cristobal, Pinar del Rio), of a febrile clinical picture with intermittent and sudden elevation of temperature, accompanied by chills and splenomegaly, suggests the possibility of malaria. With regard to the jaundice, the obstructive and hemolytic types were ruled out, because there was bile in the urine, the intensity of the jaundice, the rubinic discoloration of the skin, the absence of pleiochromic feces and marked urobilinuria, and a normal erythrocyte fragility. Wherefore, we classified the jaundice as hepatogenous or parenchymal in type with a possible obstructive episode at the beginning. Then the question arose regarding the etiology of this parenchymal jaundice.

Could it be considered as secondary to the malaria?

Could it be caused by a coexistent virus hepatitis, or to some other toxic or septic etiology?

The appearance and development of the jaundice at a stage of remission of the malaria, the prolonged course, the presence of an enlarged liver, are only partially explained because of the malaria itself and suggested, along with other possibilities, the diagnosis of a concomitant infectious hepatitis, but the malarial etiology could not be easily ruled out. Past history in regard to a possible contagion through plasma, sera, etc., were negative. Yellow fever, non-existent in Cuba, was easily ruled out. Other toxic or septic etiological factors could not be elicited.

The question was approached, through repeated biopsies of the liver plus a serial study of liver function, which, we thought, would also add to the knowledge of the malarial liver.

#### SPECIAL FINDINGS

The thick blood film, performed right after his admittance, was positive, demonstrating the presence of numerous schizonts of *Plasmodium Falciparum*, with absence of gametocytes. Blood count and Wintrobe indexes showed a mild hypochromic

anemia. Leukocytes 8.5 with granulocytes 69 per cent, lymphocytes 20 per cent, and monocytes 11 per cent, these showing a reticuloendothelial reaction. Erythrocyte fragility was normal. Urine was positive for bile pigments and bile salts. Normal blood urea and glycemia. Kahn negative. Fluoroscopy of the thorax was normal.

The findings of the liver function tests, performed before treatment were similar to those commonly found in hepatogenous jaundice, showing a moderate liver insufficiency. The qualitative direct and indirect Van den Bergh reactions were both positive. The total bilirubin was 5.32 mg. per cent (Malloy-Evelyn), the quantitative direct reacting fraction was 3.32 mg. per cent with an index of 0.62, as observed in benign acute hepatitis. Regarding other biliary function tests, the patency of bile ducts was proved with the presence of bile pigments in the feces and by duodenal drainage. Repeated biliary drainages demonstrated a poorly functioning gall bladder not showing microscopic cholesterol crystals or calcium bilirubinate. There was slight urobilinuria. Takata-Ara and Hanger (48 hours reading) flocculation reactions, were both positive though colloidal gold reaction (Gray) and Weltman were nearly normal. Bromosulfalein retention (5 mg. photoelectric reading) was of 65 per cent at 5 min. and of 18 per cent at 45 min., evidently positive, meaning a liver cell insufficiency. Total blood cholesterol was slightly increased with a poor esterification (40 per cent). Gastric juice was practically normal. Roentgenology of digestive tract was normal.

The first liver biopsy was performed on admission. The Vim-Silverman needle was used, through the intercostal approach in the anterior or mid-axillary line. A good specimen was obtained. Some areas showed acidophilic coagulation cytoplasm and diffuse cloudy swelling of the hepatic cells, with pyknotic nuclei, moderate periportal round cell infiltration, hyperplasia of reticuloendothelial tissue, showing melanic or black pigment in Küpffer cells, and dilatation of the sinusoids with loss of outline (Fig. 1). In brief, the first biopsy showed: acute hepatitis, moderate pre-fibrotic periportal infiltration and an evident reticuloendotheliosis with the presence of the specific malarial pigment. Turnbull ferric reaction was performed with negative results. Parasites were not seen in the liver.

#### CLINICAL COURSE

Malarial treatment was established following E. Llanio's method, administering 0.3 gram of quinine sulphate every four hours during four consecutive days (total of 1.8 grams daily). Simultaneously, a Patek-Post liver protective diet with B complex and intravenous glucose were given.

The progress of the patient was excellent. Fever disappeared 36 hours after the beginning of the treatment with quinine and was not followed by a relapse. The general condition improved. The jaundice disappeared 30 days after admission, with a return to normal of the total bilirubin. Periodic abdominal palpation demonstrated a gradual reduction of both liver and spleen enlargement. The palpation of the abdomen performed two months after admission, showed a normal liver and perhaps the lower pole of the spleen could be felt on deep inspiration.

Comparative evaluation of liver function was done, repeating the tests 10, 29 and 40 days after the patient admission, as shown in Table 1.

Quantitative and qualitative bilirubin became normal. Slight urobilinurea remained throughout the period of observation. Takata reaction became normal, but the cephalin-cholesterol (Hanger) flocculation test reduced to 1 plus, increasing again in the last test to 3 plus. Colloidal gold reaction (Gray), which was moderately positive in the beginning, became strongly positive in further tests, to decrease again in the last test, showing a flocculation only in the last tubes, without a satisfactory explanation. The thymol turbidity (Mac Lagan) was only performed after treatment and remained slightly positive in two occasions corresponding to 29 and 40 days after treatment. Bromsulfalein retention (45 min. reading), became normal 10 and 40

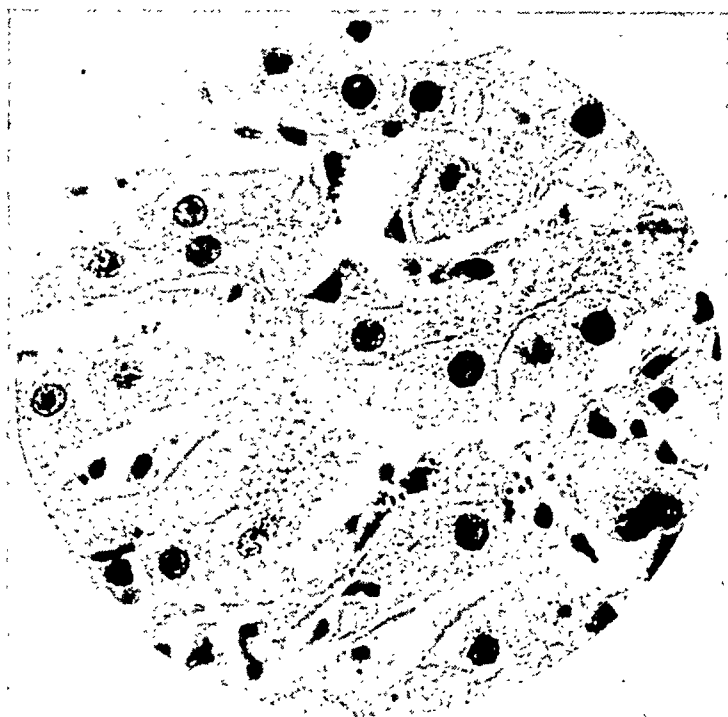


FIG. 1. Melanic or Malaria pigment in Kupffer cells of liver. Dilatation of sinusoids. (First biopsy, on admission.)

days after treatment, though the 5 min. reading was moderately positive within the same period of time. Cholesterol esterification remained positive (39 per cent).

Comparative evaluation of liver pathology through the deep liver biopsies performed 16 and 50 days after treatment showed the persistence of histological pattern though the liver cell lesions diminished from the first to the second biopsy, increasing again in the third biopsy. The infiltration of the portal islets with fibrosis increased from the first to the second biopsy (Fig. 2). Kupffer cells, malarial pigment and sinusoid alterations increased also from the first to the second biopsy, decreasing in the third. Parenchymal loss of architecture with degeneration was still found in the third biopsy 50 days after treatment, at which time the patient was in an excellent clinical condition.

TABLE 1  
*Liver Functional Tests*

SERIAL DATES	VAN DEN BERGH DIRECT	VAN DEN BERGH INDIRECT	TOTAL BILIRUBIN (M.E.)	INDIRECT BILIRUBIN	DIRECT BILIRUBIN	MALLOY EVELYN INDEX	GRAY	TAKATA	HANGER	WELTMAN	THYMOL TURBIDITY	BROMSULFALEIN	TOTAL CHOLESTEROL	CHOLESTEROL ESTERS	CHOLESTEROL INDEX
February 23, 1948 On admission	Positive prompt	Positive 2 plus	5.32 mlgr. %	2.	3.3	0.62	5500000000	3 plus	4 plus	8	—	18% (45') 65% (5')	—	—	—
March 4, 1948 10 days after treatment	Positive prompt	Positive 1 plus	4.10	1.9	2.1	0.59	5555555522	3 plus	4 plus	7.5	—	5% (45') 45% (5')	—	—	—
March 23 29 days after treatment	Negative	Positive 1 plus	0.67	—	—	—	5554300000 5554115555	Neg.	1 plus	7	6 U	—	250	100	40%
April 3, 1948 40 days after treatment	Negative	Positive 1 plus	0.32	—	—	—		1 plus	3 plus	7.5	10 U (30') 9.5 U (18') Shay 95%	6% (45') 30% (5')	240	95	39%

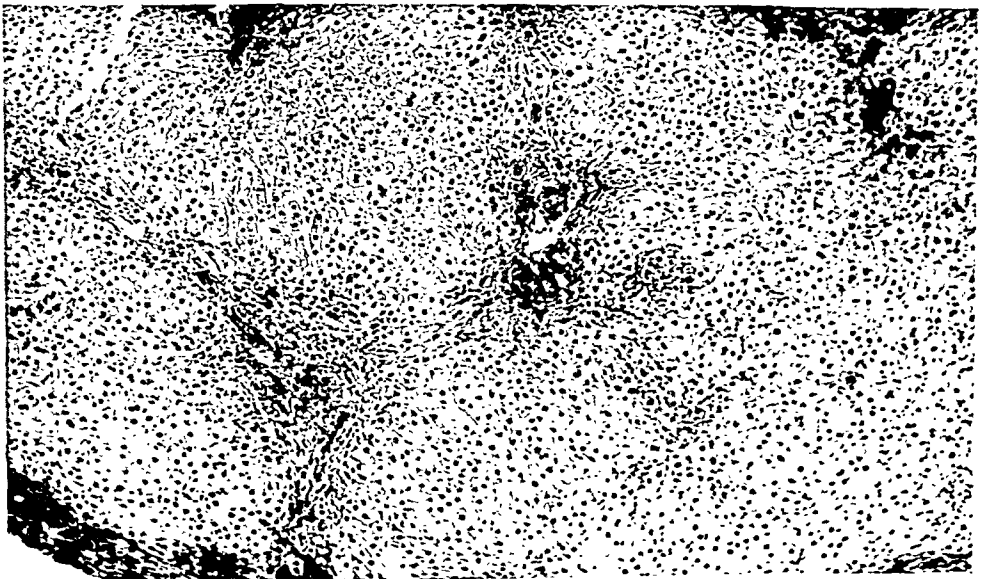


FIG. 2. Infiltration of portal islets are shown. (Second biopsy, 16 days after admission.)

## DISCUSSION

The diagnosis of malaria was confirmed without doubt by the blood smear and the existence of an hepatogenous jaundice is undoubtedly proven by the results of the liver function tests, biopsies and bile pigment determination in the blood and urine.

The liver enlargement present in our case does not prove anything in favor of either etiology since it is of common occurrence in both malaria and virus hepatitis.

The possibility of an hepatic jaundice of malarial etiology must be accepted, at least on theoretical grounds, as a result of the combined action of a number of factors; malarial parasite toxins, lesions of the intrahepatic vascular and reticuloendothelial systems and damage to the cells in malarial hyperhemolysis. The incidence of hepatic jaundice in the course of malaria, is nevertheless very low in our experience, and referred to in medical literature as a rare phenomenon; Kern et al, point out these facts. Eppinger states that in his opinion, only the existence of a previous liver damage may condition the appearance of an hepatic jaundice in malaria. Rieux accepts the possibility in severely complicated cases. Lichtman points out the frequency of subclinical jaundice caused by different etiological factors. Hills, in a series of 8,831 cases of malaria, found jaundice in only 24, with higher frequency in the falciparum type. Williams deals with the possibility of hepatogenous jaundice in the course of experimental malaria. Read et al, found in experimental malaria only a 4 per cent of hepatogenous jaundice, more severe in vivax type, with a duration of about 15 days.

The liver function tests, do not have differentiating value per se, the results being similar in both possibilities. Fairley points out the positive results of galactosuria and bromsulfalein retention in benign and malignant malaria with liver insufficiency. Lichtman quotes the presence of a low value for cholesterol esters in malaria, but the thymol turbidity and cholesterol esterification are very often changed in viral hepatitis. Popper and Franklin state that in virus hepatitis, the cephalin-cholesterol flocculation and thymol turbidity reaction are positive with more frequency and intensity than in toxic hepatitis.

The histological pattern of our case, has features common to both malarial liver and the lesions of virus hepatitis. The hyperplasia of the reticuloendothelium, loss of outline of the sinusoids, and changes of Küpffer cells with deposition of a large quantity of pigment\* in round well outlined masses, are well

\* The black, brown, melanotic or malarial pigment, has been described by Fairley, Jonesco and Kelsh, as a specific element of this disease. Mostly, it is found in Küpffer cells or in the so called melaniferous mononuclears and Danilewsky considers, that it originates from the parasite catabolism, rather than from the hemoglobin. It has no iron in its molecule, but a final criterion is not known. Also hemosiderin is found in malarial liver.

known features of the malarial liver, as described by different European and American authors (Chauffard, Trabaud, Mackie, Schiff and others). Evident malarial cirrhosis, according to most authors (Fairley, Tirimurti, Sereffetin and others) requires a previous or coexistent etiological factor.

We have also had the opportunity to study the liver biopsies of two other cases of malaria without jaundice in which similar histological changes were found. Popper and Franklin state also, that in virus hepatitis perhaps a stronger inflammatory reaction is observed in biopsy as compared to toxic types of hepatitis.

In this case, as on many other occasions before, we found it hard to correlate the biopsy findings with the changes in liver function tests. We have observed in our case some late hepatic lesions through liver biopsy and some borderline positive results in liver function tests, 40 days after jaundice subsided, with a fair clinical condition of the patient. We have lately done serial studies in a number of cases in an effort to correlate the biopsy findings and liver function tests in the active stage and late periods of hepatitis.

The progress of our patient after treatment has given an opportunity for speculation in regard to the etiology of his jaundice without definite conclusions. Nevertheless, we favor the possibility of an acute viral hepatitis in coexistence with the malaria.

#### SUMMARY

We are presenting a case of plasmodium falciparum malaria, associated with a hepatogenous jaundice and hepato-splenomegaly.

The etiological relationship between the jaundice and the malaria or a co-existent virus hepatitis is discussed, suggesting the possibility of the coexistence.

The evaluation of liver functional tests and deep liver biopsies, is made to clear up the etiological dilemma and to contribute to the study of the late manifestations of acute viral hepatitis.

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## PEPTIC ULCER IN INFANCY

### REPORT OF A CASE WITH HEMORRHAGE AND PERFORATION

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Aside<sup>1</sup> from experimental investigation, practically all that is known about peptic ulcer has been gathered from the study of individuals in the early and middle decades of life. Until recently but little attention has been given to the disease as it appears in the extremes of life. It is likely that a careful study of cases of ulcer appearing in infancy and childhood will afford data that may be helpful in a better understanding of the disease as it occurs in later life.

Judging from the literature it may be assumed that peptic ulcer is a rare disease in infancy and childhood. According to Hutchins,<sup>1</sup> there had been reported in the world literature up to 1944 only 243 cases. Up to the same period only 77 cases of perforation had been reported. Brinkman, as quoted by Wamberg,<sup>2</sup> observed ulcers in eleven patients under twenty years of age (0.2%) in 5,493 autopsies of ulcer in all age groups. Kennedy<sup>3</sup> reported only three children among 10,000 patients admitted to the Mayo Clinic for the treatment of peptic ulcer. However, 42 of the last 2,000 patients had had symptoms dating back to childhood.

Duodenal ulcer appears to be at least three times more frequent in infants than gastric ulcer. Either may be complicated with hemorrhage or perforation. That age may be of little importance however, in any consideration of ulcer, is attested by the fact that it occurs in the unborn child<sup>4</sup> as well as in those approaching the turn of the century.<sup>5</sup> Concerning the sex incidence it is of special interest that in 1928 the ratio in male and female according to Berglund<sup>6</sup> was 1.5 to 1.0, the difference in incidence being greater in the later age groups, while in 1946 the ratio, as reported by Kaijser<sup>7</sup> was 8 to 1 in a similar Scandinavian group.

As ulcers in infants are apt to be of an acute variety, terminating rather suddenly with hemorrhage or perforation, little opportunity is afforded for clinical study of such cases. For this reason the following case is reported in detail because the child was in the hospital for a prolonged period and the course of the disease could be carefully observed.

### REPORT OF CASE

*Case 1.* R. B., a male negro infant, one month of age, was admitted on May 30, 1947 to the Philadelphia General Hospital on the service of Dr. Paul Györgi. Birth history was normal and birth weight was 6 lbs. 4 oz. The baby had been on an ade-



quate evaporated milk formula. Orange juice and cod liver oil had not been started. Prior to admission he had received, since he was one week old, thirteen drops daily of a proprietary laxative, known to contain cathartic acid.

The infant appeared to be well until the day before admission when he developed vomiting and diarrhea. The vomitus consisted of undigested milk. The stools were soft and of a yellowish-green color.

Physical examination on admission revealed an extremely malnourished and dehydrated infant with oral thrush. Weight was 5 lbs. 12 oz. Temperature was normal. The CO<sub>2</sub> was 12 volumes per cent.

The infant was put on parenteral lactate and saline, being given nothing by mouth for the first twelve hours. The CO<sub>2</sub> rose to 47 volumes per cent. He was then given glucose-saline water by mouth for the next thirty-six hours followed by a dilute skimmed milk formula.

For the first nine days in the hospital the child continued to suffer a mild diarrhea having two to six semi-liquid yellowish-green stools. During this time he received a dilute skimmed milk formula and parenteral glucose, saline and plasma. Fluid intake was adequate. The caloric and protein intake however were only about 50 per cent of normal requirements—averaging 200 calories and 6.0 grams daily, respectively.

It was noted at this time that ulcers had developed over the scalp and ankle areas where continuous intravenous injections had been given. The ulcers failed to heal all through the baby's course in the hospital. They were irregular, sharply marginated and involved the subcutaneous fatty tissue.

On the eighth hospital day the infant became lethargic and appeared extremely weak. The rectal temperature was 95°F. The blood count revealed a hemoglobin of 10 grams and an erythrocyte count of 2,230,000. A blood transfusion was given and repeated on the thirteenth, twentieth, twenty-first and twenty-second days of admission. The hemoglobin remained at 10.4 grams while the erythrocyte count rose to 3,420,000. The leukocyte counts were normal throughout. The temperature varied from a low of 95°F. to 103°F. for a few days and then remained normal.

By the tenth hospital day the diarrhea had subsided and the oral intake had improved and the formula was graduated to that of whole milk. At this time the infant attained his maximum weight of 6 lbs. 4 oz. On the twentieth day the diarrhea recurred with seven yellowish-green liquid stools daily. Glucose-saline mixture was substituted for the feedings for twelve hours. This was then alternated with small feedings of skimmed milk. In a few days the stools decreased to three daily.

On the twenty-seventh hospital day the patient suddenly passed a voluminous dark red bloody stool, this being the first evidence of any bleeding into the gastrointestinal tract. Abdominal examination revealed hypoperistalsis and palpable dilated loops of bowel. The infant was taken off oral feedings and a 60 cc. blood transfusion given. Sixteen hours after the bloody stool was noted the infant vomited blood. He then became progressively weaker and died seven hours later on June 26, 1947.

Postmortem Examination: The peritoneal cavity contained a considerable quantity of fresh blood and stomach contents. Peritoneal surfaces were smooth and

shiny. Pointing toward the liver, just distal to the pyloric ring, was a perforated duodenal ulcer about eight millimeters in diameter. The ulcer, as viewed from with-

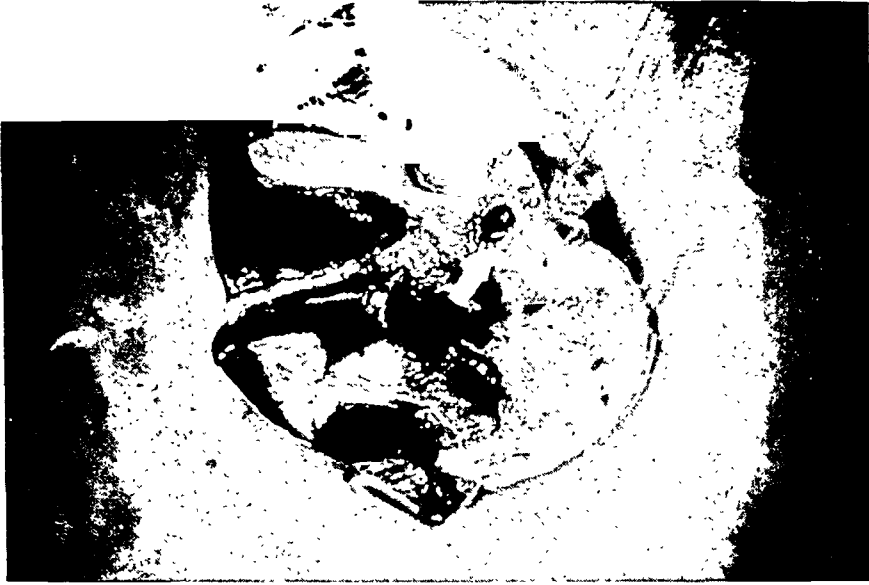


FIG. 1



FIG. 2

in, presented edges which were thickened and fibrotic. The entire gastrointestinal tract from duodenum to anus was filled with clots of blood, bright red in the upper segments, but tarry in the region of the sigmoid.

The gross appearance of the ulcer indicated it was a chronic lesion. Unfortunately, histologic examination was not made. There were no other significant postmortem findings.

### *Etiology*

In general the patients are characteristically marasmic. It is debatable whether their state of malnutrition is the cause or result of their disease.

As is the case with adults there is a difference of opinion concerning gastric secretion in infants and children. Repeated investigations have shown that all the glandular elements found in the gastro intestinal mucosa of adults are present at birth.<sup>8</sup> It has been shown by Miller<sup>9</sup> that the full term infant shows on the first day of life an average of twenty-seven degrees of free acid; the premature infant an average of twelve degrees. Miller has also shown that this figure falls to zero by the eighth day, with free acid reappearing towards the end of the second week, and then rising to only an average of two degrees by the fourth week, remaining at a low level throughout infancy. The average adult response as shown by VanZant et al.<sup>10</sup> is then not reached until the age of twenty. Kaijser<sup>7</sup> believes that the free acid secretion in children of all ages is as high as in adults.

Disturbances of the circulation have long been thought to be the primary factor in ulcer production. In infants such a relationship can frequently be demonstrated. Asphyxia, the result of prolonged and difficult labor may lead to devitalization of the gastric mucosa and thereby favor ulcer production. This is particularly probable in neo-natal cases in which histologic examination of the ulcer reveals necrosis and hemorrhage into the surrounding tissue without any associated inflammation. A striking characteristic of most peptic ulcers in infants is the absence of any inflammatory reaction—the lesion being mainly destructive and showing little evidence of repair. Boles, Riggs, and Griffith<sup>11</sup> have demonstrated the existence of disturbances of the circulation that appeared significant in the etiology of ulcer in adults and may well be applicable to infants.

Gastric irritants have long been suspected of playing a part in the cause of ulcer. Hurst and Stewart<sup>12</sup> reported a case following ingestion of caustic fluids. One of Guthrie's cases followed an overdose of castor oil. In the first of our reported cases a laxative containing cathartic acid which is the active ingredient of senna had been given each dog since one week of age.

Infection, malnutrition, fever and trauma are all incriminated in causing ulcer in infancy as in adults. Of interest in connection with infection is the report by Berglund<sup>13</sup> of six cases of meningitis associated with peptic ulcer.

### *Symptomatology*

In the newborn, the onset is usually sudden without any premonitory symptoms, the great majority suffering from perforation or hemorrhage. Such complications manifest themselves by melena, shock and distension. Except in a few cases there is no evidence of intracranial injury or sepsis. Later, in the first two years of life, while the majority of cases bleed grossly or perforate, there are often premonitory symptoms such as anorexia, evident abdominal pain, hematemesis or melena which may occur over a period of weeks or months before serious symptoms appear. Pyloric obstruction is seen occasionally, and may be mistaken for congenital, hypertrophic pyloric stenosis.

### *Prognosis*

The prognosis in complicated ulcer requiring surgery is not good. Bird, Limper and Mayer<sup>14</sup> reviewed one hundred and nineteen operated cases that had been reported by 1941. The operative mortality in the newborn was eighty per cent; in the age period of fifteen days to one year it was sixty per cent; in the two to six year group there were no deaths; in the seven to eleven year group, the mortality was seven per cent. The youngest case with successful operation reported was a thirty-four and a half hour old baby with perforated ulcer.

### *Treatment*

As has been repeatedly stressed in the literature the first essential in the treatment of ulcer in infancy is to recognize the fact that infants are subject to the disease and perhaps suffer from it more frequently than we suspect. When perforation, repeated hemorrhage or obstruction occurs, operation is almost always indicated. Closure of perforation, gastrojejunostomy or resection are done, depending on the age and condition of the patient. Gastrojejunostomy appears to be the operation of choice in infants. Marginal ulcers occasionally occur following the operation, but apparently not with the same frequency as in adults.

### SUMMARY

A case of peptic ulcer in infancy is presented with postmortem findings. In this case hemorrhage and perforation had occurred. The etiology, symptomatology and treatment of peptic ulcer in infancy are briefly discussed.

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## HEREDITARY HEMORRHAGIC TELANGIECTASIS\*

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Hereditary hemorrhagic telangiectasis has been adequately discussed and the literature amply reviewed by recent writers.<sup>1-3</sup> These cases are reported because lesions were seen by gastroscopy, confirming recent similar reports in the literature,<sup>4-7</sup> and because in one case there was a concomitant finding of spina bifida occulta. The criteria for diagnosis of the disease have been met adequately: They consist of the triad of (1) hereditary history, (2) tendency to epistaxis, starting in childhood, and (3) later development of telangiectases of typical number and distribution.

### CASE REPORTS

*Case 1.* H. E. H., a 57-year-old trainman was readmitted to the hospital on 11 June 1946 complaining of frequent epistaxis, and of pains in his epigastrium and low back. The epistaxis started in childhood, but was said to have subsided somewhat in adult life. In 1933 the patient underwent a tonsillectomy and a submucous resection, following which he had daily, profuse hemorrhages for many years. These have subsided, but he still has some blood loss almost daily. The stimuli for epistaxis are numerous and non-specific. The first episode of epigastric pain was claimed to have started while in France in 1918, and the patient has had frequently recurring episodes since then, with almost continuous pain since 1939. This pain is localized and burning, starts about four or five o'clock in the morning, and is relieved by breakfast, but soon recurs and is aggravated by subsequent meals. Atropine orally has given the greatest relief, although he has been on Sippy regimen and aluminum hydroxide gel innumerable times. The patient does not know of any episode of frank melena, but since he has had a chronic anemia, he has taken iron and his stools have been persistently black. There is no history of hematemesis. The low-back pain also started while in France, following a severe attack of influenza. This pain is localized and persistent, aching in character, and has been incapacitating since 1939. In 1932 a carcinoma of the lip was treated, first by radium seed, and later by electrodesiccation. Telangiectases of the face and oral mucous membrane were first noted at this time by the patient and by a medical examiner.

*Family History:* The patient's paternal grandfather had daily epistaxes which were attributed to pipe-smoking. His father was not known to have been affected by the disease. The only sibling, a younger brother, had a massive hematemesis at the age of thirty-three years. He died very suddenly one year later, and post mortem exami-

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nation revealed no apparent cause for death. The patient's son and daughter, whom he has not seen for several years, did not have bleeding tendencies in childhood.

*Physical Examination:* The patient appeared to be a pale, chronically ill, white male, slightly older than his stated age. Telangiectases were visible on the hands, chest, lips, hard palate, base of tongue, and nasal septum. There were none seen on the lower extremities. The heart and lungs were not remarkable. The pulse was 100 and the blood pressure was 132/80. The liver edge was palpable, sharp, and tender, four centimeters below the costal margin. There was slight percussion tenderness over the lumbosacral area, but no restriction of movement. On indirect laryngoscopy the vocal cord was found to be hyperemic. *Gastroscopy* revealed about six or seven small sub-mucosal areas of redness resembling hemorrhage on the angulus and extending out to the anterior wall. Each of these measured about 3 millimeters in diameter and there was no associated defect in the mucous membrane. On the posterior wall, where visibility permitted, were seen similar submucosal reddish spots, almost all of which lay on top of folds. The gastric mucous membrane otherwise appeared quite normal. A second gastroscopy, performed one week later to eliminate the possibility of artefact, revealed essentially the same findings. Sigmoidoscopy to 15 centimeters revealed no telangiectases. X-rays of the chest, upper gastrointestinal tract and gallbladder were normal. Antero-posterior and lateral films of the lumbosacral joints showed a marked congenital defect of the 5th lumbar vertebra. The neural arch had failed to close and there was a defect through the laminae on each side. The 5th lumbar vertebra was displaced slightly forward on the 1st sacral segment and the posterior joint space had been considerably narrowed. X-ray diagnosis: First degree spondylolisthesis and congenital anomalies of the 5th lumbar vertebra.

*Laboratory Examinations:* Urinalysis was normal. There were 2.99 million RBC with 8.6 grams of hemoglobin, and 6,800 WBC, of which 93 per cent were segmented. The sedimentation rate was 12 millimeters per hour. The reticulocyte count was 5 per cent. The platelet count, bleeding, clotting and prothrombin times and the tourniquet test were all normal. Examination of the sternal marrow revealed a normoblastic and pronormoblastic hyperplasia.

*Case 2.* H. C. C., a 42-year-old white married salesman, was admitted to the hospital on 13 June 1947 complaining of weakness, pallor, and frequent epistaxis, which had begun one month before. Therapy with anticoagulants and hematinics had failed to produce a remission in either the bleeding or the anemia. Questioning revealed a history of frequent episodes of epistaxis in childhood. In 1940 he had a severe episode which required two months of therapy for a satisfactory response. Another episode in 1945 required hospitalization in the San Diego Naval Hospital. There was no history of abdominal pain, hematemesis or melena.

*Family History:* The patient's mother had a similar condition throughout her life and was well studied at several large clinics. However, the patient had never been informed of his mother's diagnosis or of its familial implications. The patient's

eight-year-old son also had a history of frequent epistaxis, and examination revealed a few telangiectases, but his daughter appears to be unaffected.

*Physical Examination:* The patient was a comfortable white male of stated age who appeared moderately anemic. There were no positive findings other than telangiectases on the inner margin of the lip, on the tip of the tongue and on the pads of the fingers. *Gastroscopy* revealed two telangiectatic areas with irregular borders lying on top of two folds just beneath the cardia on the greater curvature. The following criteria were offered to differentiate these lesions from trauma: 1. The region was pro-



FIG. 1. X-ray of lumbo-sacral spine showing defect of neural arch of fifth lumbar vertebra in case 1.

tected from direct trauma by its position, 2. the plane of the lesions was at right angles to and not parallel with the axis of the stomach and 3. there was no erosion or active bleeding. Sigmoidoscopy to 25 centimeters revealed no telangiectases, although hypertrophied anal papillae and thrombotic external hemorrhoids were noted. X-rays of the chest and upper gastrointestinal tract were normal.

*Laboratory Examinations:* Urinalysis was normal. There were 3.5 million RBC with 9.1 grams of hemoglobin, and 8,200 WBC with a normal differential. The reticulocyte count was 2.1 per cent. The platelet count, bleeding, clotting, and prothrom-





FIG. 2. Drawing of the antral mucosa in Case 1. The telangiectases are drawn slightly larger than they actually appeared in the patient.



FIG. 3. Drawing of the cardia in Case 2.

bin times and the tourniquet test were all normal. A study of the sternal narrow showed a normoblastic and pronormoblastic hyperplasia.

#### DISCUSSION

Cases of hereditary telangiectasis have been reported with the typical lesions in almost every organ. Hematemesis and melena in excess of that which could be accounted for by the degree of epistaxis early called attention to the gastrointestinal tract. In one of his first cases Osler<sup>8</sup> reported the finding at post mortem of a carcinoma and 12 telangiectases in the gastric mucosa. Boston<sup>9</sup> and others reported cases in which dilated veins and telangiectases were found at surgery. In 1939 Renshaw<sup>4</sup> presented the first gastroscopic report of gastric telangiectases. Wolfsohn<sup>5</sup> in 1944, Rundles<sup>6</sup> in 1945 and Kushlan<sup>7</sup> in 1946 reported three further cases with gastroscopically observed lesions. The lesions noted by Renshaw were millet seed to pinhead size, brilliant red, circumscribed and caught the high-light as if slightly raised. Wolfsohn's lesions are described as red areas, like purpuric spots, bright red and not raised above the surface, varying in size between 0.1 and 0.4 cm. in diameter. Rundles records the lesions as circular, again circumscribed, two to three millimeters in diameter, intensely red, and level with the mucosal surface. Kushlan describes two types of lesions, the first a cherry angioma and the second an ecchymotic telangiectasis. He points out that Osler<sup>8</sup> demonstrated three types of skin angiomata; the first, a pin point capillary angioma, normally present in most individuals, the second a nodular nevus one to five millimeters in diameter, sessile or pedunculated, and common on the back, and third, a spider angioma formed by three or four veins converging to form a central vessel, often with a bright projecting central nodule. In our cases the lesions were purpuric spots, with irregular borders, probably comparable to the spider angioma. Cases with gastric hemorrhage but no pain or other gastrointestinal symptoms were reported by Boston<sup>9</sup> and others. In a recent review Gambill<sup>10</sup> presented a case of recurring gastrointestinal hemorrhage, but he emphasized the rarity of gastrointestinal bleeding in this disease. Neither of our patients ever had definite evidence of melena and none of the cases in which gastroscopic lesions were found demonstrated oozing from the observed lesion. On the other hand, it should be pointed out that although gastric bleeding may be suspected, the lesions may not always be demonstrated. Griggs and Baker<sup>11</sup> report a case with severe repeated hematemesis and melena, in which gastroscopy eight months after an acute episode failed to demonstrate the lesions. Kushlan<sup>7</sup> recently reported good therapeutic response to the drug rutin. This drug is reported to strengthen the capillary wall. In view of the known tendency of this disease to have remissions and exacerbations the improvement attributed to the use of the drug must be observed further. At

present both of our patients are on rutin therapy, and it is too early to make any definite conclusion. However, the first patient has observed no decrease in either the frequency or duration of his hemorrhages after six months on twenty milligrams three times daily.

The first case has additional significance because a number of apparently unrelated symptoms and their associated diseases are present on a common basis of defective constitution. The existence of multiple constitutional defects has been frequently demonstrated, and may, in fact, be the rule rather than the exception. Spinal defects have been reported previously; Weber<sup>12</sup> presented a patient with telangiectasis who also had rudimentary cervical ribs associated with camptodactylia and muscular atrophy of the hands. Singer and Wolfson<sup>13</sup> report an unexamined patient with complete spina bifida, the child of an individual with telangiectasia who had married a cousin in the same family who was apparently unaffected. There is no note made of the observation of telangiectatic lesions in this child. No other reports of an associated spina bifida have been found in the literature.

#### SUMMARY

1. The previously described gastric telangiectases in patients with hereditary hemorrhagic telangiectasis are confirmed in these two cases.

2. An established case of hereditary hemorrhagic telangiectasis with concomitant spina bifida occulta is presented.

3. The well established tendency for multiple constitutional defect is again demonstrated.

4. A therapeutic trial of rutin is being made in both cases, but it is appreciated that a prolonged period of observation will be necessary in order to offer a reliable conclusion.

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## REGIONAL ENTERITIS AND AMYLOIDOSIS

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### INTRODUCTION

In this report we wish to record generalized amyloidosis as a rare and significant complication of regional enteritis. In the clinical and post mortem files of The Mount Sinai Hospital we have been unable to find a case in which the two diseases were associated. However, in one case microscopic examination of the organs revealed the presence of minimal amyloid, found only in the malpighian corpuscles of the spleen. Crohn,<sup>1</sup> in his extensive experience with this disease, has never encountered regional enteritis and amyloidosis in the same patient. Likewise, a survey of the literature has failed to reveal a single instance of their simultaneous occurrence. The essential clinical and pathologic data of our case follow.

### REPORT OF CASE

*Clinical Abstract.* H. M. (Adm. no. 557269), a woman 33 years of age, had been observed continually for 11 years in the wards and out-patient department of The Mount Sinai Hospital. She was first admitted to the hospital in February, 1936 because of persistent lower abdominal cramps, daily fever to 101°F., and bloody diarrhea, which had been present for about one month. Except for pallor of the skin and mucous membranes nothing noteworthy was found on the physical examination. The blood pressure was 106/62 mm. of mercury. There was a hypochromic anemia, moderate elevation of the white count, and a normal differential. The urine was normal, and the stools were guaiac positive. Sigmoidoscopy revealed mild inflammatory changes of the rectum and sigmoid. Barium enema was normal; the terminal ileum was not visualized. Chemical examinations of the blood showed normal values for urea nitrogen, serum proteins, albumin-globulin ratio, and cholesterol. She responded well to symptomatic therapy and whole blood transfusions. Thereafter she continued to have irregularly recurrent bouts of diarrhea, separated by weeks to months of normal bowel movements. In January, 1937 an attack of diarrhea was associated with erythema nodosum.

In April, 1938 an appendectomy was performed because of severe right lower quadrant pain, fever, nausea, vomiting, and leucocytosis. At operation the appendix was found to be thickened and inflamed, and the terminal ileum and mesentery were thickened and indurated. The findings in the terminal ileum were interpreted by the surgeon as non-specific regional ileitis. Pathologic report on the appendix was acute and chronic appendicitis. Postoperative convalescence was uneventful.

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She continued to have episodes of diarrhea, abdominal pain, and fever. The anemia increased in severity and became more refractory to therapy. Examinations of the gastrointestinal tract by barium meal and enema in 1940 and 1941 revealed irregularity, distortion, loss of distensibility, and narrowing of the terminal 9-15 cm. of the ileum. The remainder of the small bowel and the colon showed no abnormality.

During 1945 and 1946 edema of the ankles appeared and gradually progressed to anasarca. The liver and spleen were palpable. The blood pressure was 125/88 mm. of mercury. Anemia, leucocytosis and lymphocytosis were present. The urine contained large amounts of albumin, a few red cells, white cells, and hyaline casts. Chemical examinations of the blood (values per 100 cc.) were as follows: serum proteins 4.1 gm. (albumin 1.8 gm. and globulin 2.3 gm.), total lipids 906 mg., and cholesterol 420 mg. There was no azotemia. Liver function tests were normal. Congo red test showed 75 per cent disappearance of the dye from the blood in one hour. The basal metabolic rate was minus 21. Examination of the gastrointestinal tract by barium meal demonstrated a stenotic loop in the lower jejunum with loss of normal mucosal pattern in the adjacent loops of ileum. Liver biopsy failed to reveal evidence of amyloid disease. She responded well to dietary control, crude liver and diuretics and was discharged with slight dependent edema.

The final admission in December, 1946 was precipitated by the signs and symptoms of acute peritonitis. She was dehydrated, and there was slight dependent edema. The hemogram and urinalysis were essentially unchanged. Chemical examinations of the blood revealed no significant alterations from the preceding results except for the increase of urea nitrogen and creatinine to 72 and 6.1 mg. per 100 cc. respectively. Azotemia increased, edema became more severe, and convulsive episodes occurred. She died on the sixth hospital day with the clinical manifestations of uremia, generalized peritonitis, and terminal congestive heart failure. The renal disease was interpreted as either chronic glomerulo-nephritis or amyloidosis.

From the time of the first hospital admission the stools were repeatedly guaiac positive and did not reveal pathogenic bacteria, ova or parasites; agglutinations of the blood for dysentery were constantly negative.

*Postmortem Examination* (Autopsy no. 13567). There was generalized pitting edema, most pronounced in the extremities and dependent portions of the trunk. In the peritoneal cavity were 500 cc. of thin, odorless, turbid, brownish fluid. A fibrinous membrane coated the terminal ileum and its mesentery, ovaries, uterus, and rectosigmoid. Each pleural cavity contained 500 cc. of aqueous amber fluid. No excess fluid was present in the pericardial sac.

The proximal 50 cm. of the jejunum appeared entirely normal. In the succeeding 14 cm. there were small scattered mucosal scars and ulcerations, most prominent at the mesenteric border, which was slightly thickened. For the next 60 cm. the jejunum (Figs. 1 and 3) was diffusely and moderately thickened and rigid, with alternating areas of dilatation and stenosis, neither of which was extreme. The normal mucosal pattern was completely lost, being replaced by extensive irregular scars and ulcerations, between which were islets of flat polypoid reddened mucosa. This im-



FIG. 1. Opened segment of mid-jejunum with mesentery showing complete loss of normal mucosal pattern, extensive scarring, ridging and polypoid hyperplasia of mucosa, focal stenosis, and hypertrophy of wall.

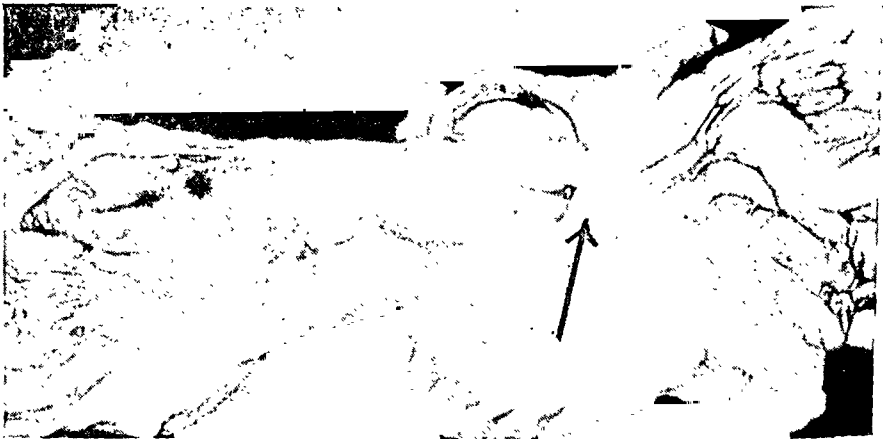


FIG. 2. Terminal ileum, ileocecal valve, and cecum. Arrow at ileocecal valve, and ileum to its left. Terminal ileum extremely hypertrophied and stenotic. Mucosa atrophic and focally puckered. Ileocecal valve and cecum normal.

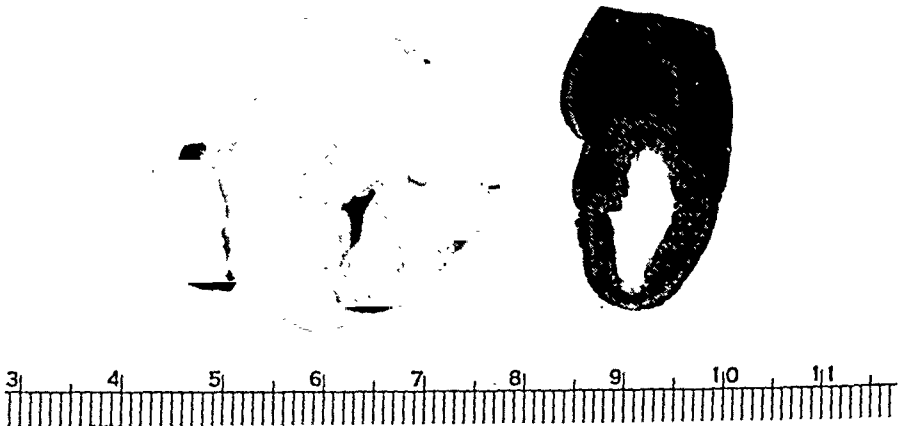


FIG. 3. Cross sections through terminal ileum (left) and mid-jejunum (right) with mesentery attached. Hypertrophy and stenosis extreme in ileum and moderate in jejunum.

parted to the surface a cobblestone appearance. At the mesenteric border were 6 non-communicating, narrow, shallow sinuses which extended in the direction of the mesentery. None of these tracts was deeper than 6 mm. The serosa was injected, roughened, and thickened. No fresh serosal exudate was present. The mesentery of the jejunum was thickened and boggy, and its lymph nodes were enlarged to 1.5 cm.

The most distal 10 cm. of the terminal ileum (Figs. 2 and 3) were exceedingly thickened and stenotic. The mucosa was atrophic and scarred. An area of 5 cm. immediately ahead of the involved distal 10 cm. showed scarring and ulceration of the mesenteric border similar to that described in the upper jejunum. Twenty-nine cm. proximal to the ileocecal valve the ileum was acutely kinked and firmly adherent to the diseased terminal ileum. Six cm. proximal to the valve was a pin-head puckered ulceration, which was in direct apposition to the point of adherence of the knuckle of ileum. The ulcer could be probed for several mm., but no gross perforation or fistula could be demonstrated. It was in this area that the fibrinous exudate coated the terminal ileum and contiguous mesentery. The mesentery of the terminal ileum was thickened and indurated, and the lymph nodes were small.

The remainder of the gastro intestinal tract was free of significant changes. Transition from healthy to diseased small intestine was rather abrupt, and the ileitis terminated sharply at the ileocecal valve, which appeared normal. Fistulae were not present.

Microscopic study of the ileum and jejunum revealed a severe, chronic, non-specific, non-granulomatous enteritis with focal superficial ulcerations. In the jejunum (Fig. 4) and portions of the ileum the inflammatory process was active, and there were moderate fibrosis of the submucosa and serosa and moderate hypertrophy of the muscularis. In the terminal ileum (Fig. 5) fibrosis of the submucosa and serosa and hypertrophy of the muscularis were extreme, and active inflammation, though present, was much less conspicuous than in the jejunum. Similar inflammation and fibrosis were present in the mesentery. The mesenteric lymph nodes showed sinus endothelial hyperplasia. Stains for bacteria yielded negative results, and no ova or parasites were found.

Smears of the peritoneal fluid and sections of the fibrino-leucocytic exudate covering the pelvic organs failed to reveal bacteria. Culture of the peritoneal fluid did not yield any growth.

The spleen, kidneys (Fig. 6), adrenal glands, and thyroid gland were severely involved by amyloid. In sections at all levels of the alimentary tract, diseased as well as normal, amyloid was present in moderate amount, being most conspicuous in the terminal ileum. Sections of virtually all other organs examined showed the presence of amyloid, which was almost exclusively limited to the walls of blood vessels. Except in the vessels there was no amyloid in the liver.

The major pathologic diagnoses were as follows:

1. Ulcerative regional enteritis involving jejunum and terminal ileum.
2. Acute fibrino-purulent pelvic peritonitis probably due to minute perforation of terminal ileum.



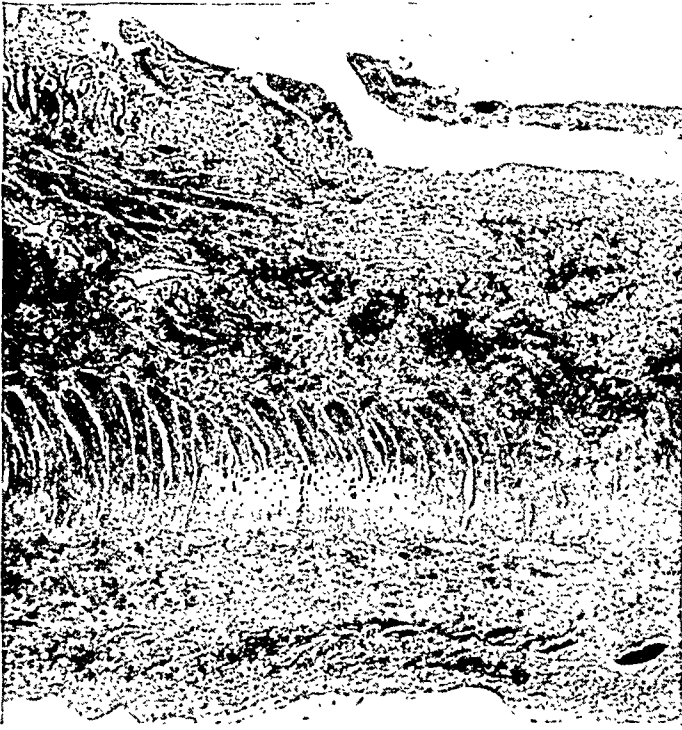


FIG. 4. Low power view of mid-jejunum showing superficial ulceration, fibrosis and active inflammation of submucosa, hypertrophy of muscularis, thickening and active inflammation of serosa;  $\times 20$

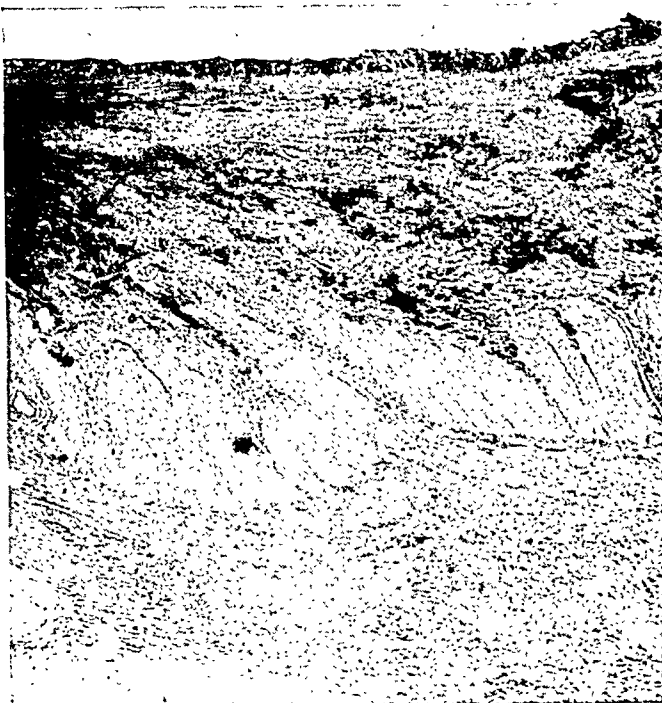


FIG. 5. Low power view of terminal ileum showing atrophic mucosa, extreme thickening and fibrosis of submucosa and serosa with minimal active inflammation, and marked hypertrophy of muscularis;  $\times 10$ .

3. Generalized amyloidosis with severe involvement of kidneys, spleen, adrenal and thyroid glands.

4. Anasarca.

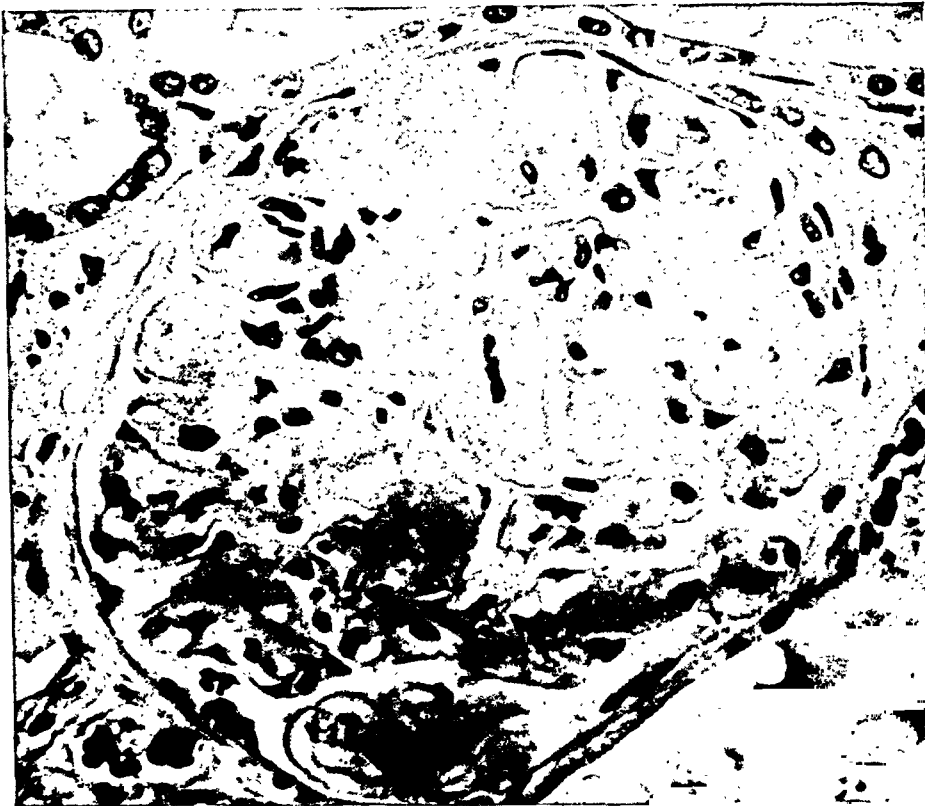


FIG. 6. High power view of kidney. Glomerulus almost completely replaced by amyloid.

#### DISCUSSION

The clinical course of this patient was characteristic of the evolution of the enteritis originally described by Crohn, Ginzburg and Oppenheimer<sup>2</sup> as "regional ileitis." Roentgen examinations and the identification of an inflammatory ileal mass at operation further substantiated the clinical criteria. During life difficulty was encountered in distinguishing between renal amyloidosis and the nephrotic stage of chronic glomerulonephritis. The albuminuria rendered the congo red test difficult of evaluation, but the insignificant amount of amyloid in the liver probably accounted for the relatively low retention by the tissues of the injected congo red. The persistent albuminuria with relatively few formed elements in the urine, progressive anasarca in the absence of congestive heart failure, hepatosplenomegaly, a persistently low blood pressure, and clinical evidence of renal insufficiency militated strongly for the diagnosis of renal amyloidosis.

Pathologically there were two unique features of the intestinal involvement: (1) the presence of two widely-separated diseased segments of small intestine with relatively normal bowel intervening, and (2) the striking difference in gross appearance between the long segment of affected mid-jejunum and the small segment of involved terminal ileum. We view the disease in the terminal ileum as of long standing and typical of what we have come to recognize as terminal ileitis. We interpret the lesion in the jejunum as the more active counterpart of a morphogenetically similar morbid process, and from the standpoint of time, as of more recent origin.

The distribution of amyloid in the body, except for its absence in the liver, was characteristic of so-called secondary amyloidosis. At necropsy, there was no chronic suppuration incident to the regional enteritis, and none of the known diseases causally related to secondary amyloidosis could be found.

#### SUMMARY

Generalized amyloidosis in the course of chronic non-specific inflammatory diseases of the intestinal tract occurs with great rarity. To our knowledge, this is the first recorded instance of amyloidosis in association with uncomplicated regional enteritis. Despite careful clinical and pathological investigations of this case, no specific initiating or precipitating factor for the amyloidosis, other than the regional enteritis, could be ascertained.

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## TYPHOID-LIKE INFECTION DUE TO PARACOLON BACILLUS

### REPORT OF A CASE SUCCESSFULLY TREATED WITH STREPTOMYCIN\*

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There are increasing numbers of reports in the literature to the effect that certain members of the paracolon group are associated with cases of acute and chronic diarrhea in man. In 1945 Edwards<sup>1</sup> reported the isolation of a paracolon bacillus from colitis in an infant. Since then several outbreaks of gastroenteritis have been attributed to paracolon organisms.<sup>2-4</sup> Luippold<sup>5</sup> has described a case of chronic enterocolitis associated with a paracolon bacillus which was apparently cured by streptomycin therapy. More recently Darnall<sup>6</sup> has added 18 cases of chronic dysentery associated with paracolon bacilli, five of which showed clinical cure or improvement following streptomycin therapy. We felt that the following case warrants recording because of its acuteness and severity as well as response to streptomycin therapy.

#### REPORT OF CASE

C. E., a 45 year old white male physician, was in good health until June 30, 1947, when he had several loose bowel movements with little discomfort. On the following day he felt tired and complained of aching pains in the shoulders, back and legs. Later that evening he felt feverish and at midnight experienced severe chills lasting about one hour. At 4:00 a.m. and again at 10:00 a.m. on the following day, he had two more bouts of chills of similar duration with elevation of temperature to 103 and 104°F. During this time he passed several watery, foul smelling stools. He was admitted to Michael Reese Hospital at noon on July 2nd.

On admission his temperature was 106.4°F. rectally, pulse rate 108 and respiratory rate 24 per minute. His skin was moist, and he complained of severe frontal headache and generalized weakness. Physical examination at this time was otherwise negative. The temperature for the next few days ranged from 103.4 to 101°F. in the evening with almost complete defervescence in the morning. On July 7th his temperature rose again to 104°F. at 10 p.m. Thereafter, the temperature gradually returned to normal on July 8th and has remained so. Showers of fine moist rales at the base of the lower lobe of the right lung were heard during the first few days only.

During his stay in the hospital, he continued to pass three to four foul smelling, watery stools daily until July 14th when they became mushy. Recently he has informed us that his stools remained mushy until the early part of December, 1947. From time to time he complained of abdominal pain with and without acute dis-

\* Supported in part by Michael Reese Research Foundation.

tension. At one period he suffered from severe pain in the upper right quadrant with marked tenderness. Traces of bile and bilirubinogen were detected in the urine at that time. He also complained of severe headaches and was greatly depressed for a few days. Icterus was never noted.

A bacillus belonging to the paracolon group was isolated as the predominant organism from stool specimens collected on admission and on eight additional occasions during hospitalization. No other intestinal pathogens were found. Many pus cells and a few erythrocytes were seen in wet preparation of the stools. Blood cultures taken on admission and on the following day showed no growth. Catheterized urine specimens collected on July 7 and 14 also showed no growth. His blood count on admission was 8,800 WBC, of which 75 per cent were segmented neutrophils, 12 per cent non-segmented neutrophils, 10 per cent lymphocytes and 3 per cent monocytes. The sedimentation rate was 18 mm. per hour. The Wassermann and Kahn tests of the blood were negative. Agglutination tests of serum specimens drawn on admission (July 2) and during convalescence (August 11) for typhoid, paratyphoid A and B, *Brucella abortus*, *B. melitensis* and *B. suis* were negative, as were the Weil-Felix reaction and heterophile agglutination test for infectious mononucleosis. No agglutinins for the isolated paracolon strain were detected in either specimen of serum by standard agglutination tests using saline diluent; however, a titer of 1/320 was obtained in serum collected during convalescence by means of agglutination tests using serum diluent as described elsewhere.<sup>7</sup>

Combined streptomycin and penicillin therapy was instituted immediately on admission because of the patient's severe infection of unknown etiology. One-fourth gram of streptomycin was given every three hours parenterally. Fifty thousand units of penicillin were also given at the same intervals parenterally. When the paracolon bacillus was finally identified 3 days later, penicillin therapy was discontinued. The paracolon bacillus was inhibited by 1.25 units of streptomycin when tested in vitro. Streptomycin therapy was continued for 7 days, a total of 14 grams being given. Streptomycin was stopped on July 9th at which time the patient's temperature had been normal for approximately 48 hours. The patient was started on sulfathalidine one day before streptomycin therapy was stopped and was given 15 grams four times daily. The patient was discharged on July 16, and he continued to take sulfathalidine several days after discharge. Stool specimens collected on July 14, five days after stopping streptomycin therapy, were negative for paracolon organisms. Six additional stools collected at weekly intervals and a seventh specimen collected on September 25 were also negative. Convalescence was slow and uneventful. The patient lost about 26 pounds during his illness and did not regain his former weight and strength until 5 months after discharge.

#### BACTERIOLOGICAL STUDIES

The paracolon bacillus isolated from the patient's stools collected on admission and eight additional occasions was the predominate organism on both SS agar and Endo agar plates. This organism produced colorless, smooth colonies similar to those of the typhoid-paratyphoid-dysentery group on both

media after 24 hours incubation at 37°C. Morphologically it was a gram-negative motile rod. It was not agglutinated by polyvalent Salmonella or typhoid antisera. Antigenic analysis, however, showed that this organism contained antigens for Flexner V, W, Z, Boyd 103 and Shigella schmitz.

On triple-sugar iron agar it produced an alkaline slant with acid and gas in the butt. No H<sub>2</sub>S was produced. However, H<sub>2</sub>S production was positive in the lead acetate medium of Friewer and Shaughnessy.<sup>8</sup> Glucose was fermented with acid and gas within 24 hours after incubation at 37°C. Maltose, mannite, arabinose and cellobiose were also fermented with acid and gas within 24 hours. Lactose, salicin, dulcitol and xylose fermentations were delayed 3 to 4 days. Inositol, adonitol, sucrose and raffinose were not fermented after incubation for 30 days. Acid was produced in phenol red tartrate agar. Gelatin was not liquefied, and urea was not decomposed.

This organism was methyl-red positive and Voges-Proskauer negative. Indol was produced, but citrate was not utilized. It was identified as a paracolon *Escherichia*\* because the IMViC formula<sup>9</sup> would be ++---. Its pathogenicity was tested by inoculating albino Swiss mice (Beyer strain) weighing 15 to 18 grams intraperitoneally with 0.5 cc. of a saline suspension prepared from agar slants and containing approximately 75 million organisms. All of the inoculated mice were dead within 24 hours after injection and heart's blood cultures yielded pure cultures of the same strain.

Antiserum prepared in a rabbit injected repeatedly with heat killed saline suspensions of growth from agar slants showed a titer of 1/640 for the homologous strain. The rabbit antiserum also agglutinated four additional paracolon strains isolated from cases of acute gastro-enteritis to be reported separately,<sup>10</sup> but failed to agglutinate paracolon D<sup>6</sup> kindly supplied by Major George F. Luippold of the Army Medical School. It also failed to agglutinate typhoid and Shigella alkalescens antigens.

#### DISCUSSION

In the past too little attention has been paid to the possible pathogenicity of certain paracolon organisms for man. As already mentioned there are increasing numbers of reports in the literature of the association of paracolon organisms with cases of acute and chronic diarrhea. Christenson<sup>4</sup> reported that paracolon organisms were found much more frequently in cases of gastro-enteritis in a military area highly endemic for enteric infections than either Salmonella or Shigella species. He also isolated paracolon organisms with much greater frequency in hospital cases than in normal individuals, while Salmonella and Shigella species were found with almost equal frequency in the

\* The identity of this strain has been verified by Dr. Kenneth M. Wheeler of the Connecticut State Department of Health and Mr. Kenneth Bass of the Illinois Department of Public Health.

two groups. Luippold<sup>5</sup> and Darnall<sup>6</sup> have described several cases of chronic enterocolitis with systemic manifestations which were considered functional in origin because paracolon organisms and none of the usually accepted intestinal pathogens were isolated. Streptomycin therapy in all these cases resulted in elimination of the paracolon bacilli and in clinical cure or improvement.

We feel that the etiological agent of our patient's infection was the isolated paracolon bacillus for the following reasons: First this organism was isolated in practically pure culture from stools collected on admission and on 8 separate occasions during the acute stage. No other intestinal pathogens were isolated. Secondly, the paracolon in question was shown to be sensitive to streptomycin in vitro, and the patient responded to streptomycin therapy with elimination of the paracolon from the stool as well as clinical improvement. Thirdly, the isolated paracolon was shown to contain Shigella antigens and to be pathogenic for white mice. Finally, the patient had no agglutinins for the isolated paracolon in blood serum collected during the acute stage, but he subsequently developed a titer of 1/320 during convalescence.

To our knowledge none of the paracolon infections recorded in the literature thus far have been as acute and severe as that of our patient. In a personal communication Dr. Kenneth M. Wheeler<sup>11</sup> states that he isolated paracolon bacilli on several occasions from the blood of typhoid-like cases. More recently we have studied three fatal cases in Michael Reese Hospital in which paracolon bacilli were isolated in pure culture from the blood stream or intestinal tract. These cases will be reported in a separate publication.<sup>10</sup>

Our case is the sixth reported in the literature to date in which streptomycin therapy eliminated the paracolon infection and resulted in clinical improvement or cure. Sulfathalidine therapy was started on the day before streptomycin was stopped because our patient continued to pass foul smelling, mushy stools despite clinical improvement, and in vitro tests demonstrated that the isolated paracolon strain was sensitive to sulfa drugs as well as to streptomycin. It was felt that continued streptomycin therapy might result in eighth nerve involvement or other toxic effects, while sulfathalidine would be less likely to cause reactions. Further studies are needed to evaluate sulfa-therapy of paracolon infections.

#### SUMMARY

A case report of a severe typhoid-like infection due to a paracolon bacillus (paracolon *Escherichia*) with Shigella antigens is described. The paracolon organism was isolated repeatedly from stools during the acute stage, and the infection was successfully treated with streptomycin. The patient was found to have no demonstrable agglutinins for the isolated paracolon strain during

the acute stage, but subsequently developed a titer of 1/320 during convalescence. The pathogenicity of paracolon organisms for man is discussed.

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## DISCUSSION

The following discussion of the paper by Richard B. Capps on Clinical Aspects of Sequelae of Acute Hepatitis was omitted from the November 1948 issue of *Gastroenterology*:

DR. J. EDWARD BERK (Philadelphia, Pa.): Several recent reports in the literature have implied that infectious hepatitis plays an important etiologic role in hepatic cirrhosis because of the frequency of previous jaundice in cirrhotic patients. It is manifestly difficult properly to assess the cause for jaundice occurring in the recent past in patients with cirrhosis. Even if it were granted that every episode of jaundice in the past history of these patients represented acute infectious hepatitis with jaundice, it must be shown that this incidence is significantly greater than that in the population at large if we are to infer that hepatitis with jaundice plays an important role in the production of cirrhosis. Yet, our knowledge concerning the incidence of previous infectious hepatitis with jaundice in presumably normal persons is considerably limited.

To help supply this information, a survey has been made of medical personnel at three medical schools, the University of Oregon, the University of Chicago, and Temple University. The personnel interviewed included medical students, nurses and staff physicians, all of whom were engaged in their regular duties without symptoms or obvious signs of disease. Each person with a history of jaundice in the past was carefully questioned regarding the details of the illness. Only those which appeared to conform with the usual clinical picture were accepted as instances of infectious hepatitis.

Unfortunately, the results at the University of Oregon are still not available. However, Dr. Joseph Kirsner has completed the survey at the University of Chicago and I have just finished the one at Temple University. To date we have interviewed over one thousand apparently normal people varying in age from 17 to 40 years. In this group the incidence of acceptable evidence of previous infectious hepatitis with jaundice was 6.6 per cent.

If, therefore, cirrhosis developing from infectious hepatitis occurs more than occasionally, careful history-taking in groups of patients with established hepatic cirrhosis should disclose an incidence of previous hepatitis with jaundice in significantly greater than 7 per cent, the approximate incidence in normal persons as indicated by our findings to date.

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# Editorials

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## ULCERATIVE COLITIS AND CARCINOMA

The different forms of ulcerative colitis can, in a large measure, be differentiated by examination of the lesions in the living human being. This is best done by looking at the mucous membrane through the proctoscope, but in those cases in which a colonic stoma has been made and the disease has progressed orad and in which the colonic mucosa can be studied under a hand lens, the delicate lesions on the mucosal surface show up clearly. In this so-called thrombo-ulcerative colitis, the lesions appear as a multitude of tiny discharged abscesses. In this type of ulcerative colitis, which is the commonest of all seen, even in the milder and early stages, no normal patches of mucous membrane remain. In this form there is diffuse involvement because the infection is primarily in the muscular wall of the bowel and only secondarily in the mucous membrane; whereas, in most other forms the infection is in the mucous membrane primarily and in the deeper structures only secondarily or late in the course of the disease.

The infection originates in the vessels of the muscularis mucosae and, because of thrombosis of the arterioles, countless little infarcts occur, with subsequent small mucosal abscesses. These infarcts and abscesses pepper the portion of the bowel involved, and their evacuation leaves a granular, easily bleeding mucous membrane. Involvement is never patchy. It is always diffuse. To be sure, in the most severe forms of the disease this destructive infection leaves large segments of the bowel denuded of mucous membrane but the characteristic small lesions can still be recognized in the remaining islets of mucosa. Because of the repeated onslaughts of the disease, with subsequent healing and scarring, the remaining islets of mucosa are often pinched at the base and caused to protrude into the lumen of the bowel as the so-called pseudopolyps or "polyposis cystica of Virchow."

Repeated flare-ups of the infection are followed by repeated attempts at repair, and it seems likely that the factor controlling repair may be called upon so frequently that it eventually becomes exhausted. Then a wild growth of tissue may result. Thus, multiple foci of neoplasia may follow, either in the remaining islets of the mucosa or in the deeper layers of the wall of the bowel. Such changes may occur even in young persons during the healing stage of ulcerative colitis, resulting in highly malignant cancer. Although this occurrence is a rare one, the writer has now seen more than 70 such patients. In most of them he has watched the course of the disease from the inception, through the stages of activity and healing, to the stage of carcinosis, often years later.

Various percentages for the incidence of carcinoma in ulcerative colitis have been reported, but in one of the largest series of cases the incidence was about 2 per cent. In this group, cases of polyps with a so-called grade 1 adenocarcinoma were not included, but only cases of definite, highly malignant, rapidly growing carcinoma. In such cases the carcinoma may appear in one or many foci in the wall of the infected bowel. Such carcinomas, although they may occur in only 1 case in 50, are particularly disturbing to the physician because so often they end the life of a young person in the third or even the second decade.

Some writers have tried to minimize the importance of this denouement by saying that the incidence of carcinoma of the colon after chronic ulcerative colitis is no higher than that observed in the population as a whole. They could hardly have made such a statement if they had ever seen a few dozen youngsters dying of a generalized, wildfire sort of carcinosis of the colon in the ages between 15 and 30 years. This phenomenon is so striking that after one has observed it a few times one can never think of it complacently or dismiss it as an ordinary event. It is really an extraordinary manifestation of disease.

J. A. BARGEN.

## THE LIFE SPAN OF THE INTESTINAL EPITHELIUM

The bodily conformation of an individual varies relatively slowly through periods during life, and each individual maintains rather fixed physical characteristics. It would be easy to conclude from this observation that the various tissues of the body would also be relatively stable. The results of various investigations, especially those using isotopes, indicate definitely that most of the tissues of the body, even those that have been considered most permanent, are constantly changing. The tissues of the living organism are truly dynamic, not only in respect to the processes that occur within them but also in regard to the life of the individual units. The length of life of most of the specific cells of the body is not known. The active life span of the red corpuscles is probably best understood.\*

Any observer who has studied the intestinal mucosa could not help but note the large number of cells in the crypts undergoing mitosis. No one appears to have looked into this carefully until recently, when Leblond and Stevens† studied the fate of this rapidly and constantly growing crop of new cells. They employed appropriate methods for this type of research and obtained some apparently trustworthy data which indicated some startling conclusions. They concluded that the newly formed cells in the crypts were pushed upward in an orderly fashion to become a part of the covering epithelium and to be finally ejected when they reached the tip of the villi. By computation they found that the turnover time of the whole intestinal epithelium was 1.57 days for the duodenum and 1.35 days for the ileum, or that 63.5 per cent of the duodenal epithelium and 74 per cent of the ileal epithelium is renewed per day. The results of this investigation raise several pertinent questions, among which could be mentioned the following: Why is this rapid turnover of intestinal epithelium necessary? What is the stimulus causing the formation of the new cells? What effect, if any, do the facts established have on the results of studies on fecal residue? The results of this research should serve as a stimulus for future investigations on one of the most important surfaces of the body.

FRANK C. MANN.

\* Ashby, Winifred: *Blood*, 3: 486, 1948.

† Leblond, C. P., and Stevens, C. E.: *Anat. Rec.*, 100: 357, 1948

## REFLECTIONS ON ULCERATIVE COLITIS

Certain diseases are by their very nature almost entirely surgical diseases, such as gallstones, malignancies, infections, abscesses and various other lesions; certain others, such as pneumonia, infectious diseases, cardiac states and so forth, are so obviously medical as to their management as not to require debate. Other diseases fall in the middle ground between these two states and require often discriminating judgment as to when they should continue to remain in one group, such as that of medical care, and when they move on into the other group, that of surgical care.

I know of no condition which can more quickly require removal from the medical group into the surgical group than that of ulcerative colitis, and I can think of no group of cases in which cooperation between surgeon and physician together with decisive and prompt decisions for surgery are so important in saving life. We have now dealt with well over 700 patients with ulcerative colitis and as the result of this experience, no one is more aware than we are concerning how fickle and unpredictable this disease can be as seen from either point of view, that is how unpredictable it can be in terms of unexpected remissions and how unpredictable it can be in terms of increasing seriousness, as represented by such complications as hemorrhage, perforation, intoxication and the superimposing of malignancy upon an inflammatory state.

We have had a most fortunate opportunity to acquire our experience with this disease by joint observations of a surgical service and a medical service dealing with these patients by combined efforts.

In a disease as fickle and as bizarre as this one, if it be dealt with by an individual whose interest is entirely medical or by one whose interest is entirely surgical, very definite biases and misconceptions can be established. If one deals with this disease entirely from a surgical point of view, he can readily assume that the incidence of surgical complications, hemorrhage, perforation, malignancy and such states of toxicity as to require ileostomy, is higher than it really is and so become unduly biased as to the need for surgery in these cases. On the other hand, if one deals with this disease largely from a medical point of view and has not had the opportunity to see the health-restoring effect of ileostomy followed by colectomy, or has not been impressed with the definite incidence of malignancy (in our experience 5 per cent) associated with this disease, or has not seen the hemorrhages which can result in a fatality so promptly unless aggressively approached by removal of the colon, he can fail to appreciate what, with modern methods, can be done to save and restore these patients to health and full capacity by surgical measures.

As the result of our own experience I would like to say that we have, by closer cooperation between the medical and the surgical departments, of those

patients with fevers, with passage of blood, pus and mucus and numerous daily stools, by means of earlier ileostomies, not only saved many more of these patients' lives but decreased the mortality of ileostomy, 22 per cent in our own hands in a first group down to a mortality now of 4 per cent in a later group.

I would like to call attention to the fact also that we have by aggressive approach to those patients with ulcerative colitis who are having massive hemorrhages, by early ileostomy followed by prompt colectomy saved most of them who would otherwise have been lost.

I would particularly like to remind physicians and surgeons who are dealing with patients with ulcerative colitis of the necessity of being acutely aware of the fact that approximately 5 per cent of these patients will develop malignancy, that upon any suspicion of an area within the colon, conservative measures should be abandoned and resection immediately instituted.

Most surgeons are now very familiar with the type of Koenig-Rutzen ileostomy bag that can be firmly cemented to the skin closely around the ileostomy so that skin irritation no longer occurs, so that because the bag is completely tight and can be emptied several times a day, no leakage, no soiling of clothes, and no odor occur, no unsightly bulges of the clothes are apparent and patients can conduct their lives by means of this apparatus with no limitations whatever. We have a large number of these patients who live completely normal lives and participate in any activity of life, in a few instances up to child-bearing.

For the benefit of those physicians who have had patients who have had difficulties with ileostomies such as represented so often by prolapses or retraction, I wish to call attention to the fact that technical measures have now been developed by means of which these have been largely overcome, and good functioning, satisfactory ileostomies can be established.

Based upon our own experience, probably more than half of the patients with ulcerative colitis, provided they do not develop some of the above-mentioned complications, can be handled by nonoperative measures. It is important, however, we believe, based upon our own experience and the experience of others who have been particularly interested in the surgical management of this disease, to realize that ileostomy is not the objectionable enterostomy that it was a few years ago, that surgical measures, such as colectomy, can now restore these patients to completely satisfactory and useful lives and that the mortality of the operative procedures upon this distressing disease in the hands of those experienced with it has been reduced almost to negligible figures. For these reasons I wish particularly to plead for early surgical consultations and earlier submission to surgery of those patients with ulcerative colitis in whom dangerous complications have arisen.

FRANK LAHEY.

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## Comment

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### THE TREATMENT OF CARDIOSPASM

There has been an increasing tendency to treat cardiospasm by surgical measures without first attempting to utilize more conservative measures such as dilatation of the cardia by means of hydrostatic, air or mercury dilators. Many surgeons have reported that operation, especially esophagogastrostomy, has proved of distinct value in the treatment of cardiospasm in well-selected cases. Undoubtedly, the success achieved in these cases has encouraged other surgeons to employ operation as a routine procedure. It is problematic, from the information at hand, whether such a program is actually justified or to be encouraged at this time.

The tendency to resort to operation as a primary procedure in the treatment of cardiospasm has been due in a large measure to the following misconceptions: (1) that only two thirds of patients can be completely relieved of their symptoms by forceful dilatation of the cardia and that esophagogastrostomy, on the other hand, is uniformly successful in affording relief of symptoms, and (2) that dilatation of the cardia by means of dilators, especially the Plummer hydrostatic dilator, carries with it a mortality rate of 2.8 per cent and that esophagogastrostomy is a comparatively innocuous procedure.

It is true that complete and permanent relief is obtained in only 70 per cent of cases in which cardiospasm is treated by hydrostatic dilatation and that the symptoms continue or further difficulty with deglutition develops in approximately 30 per cent of cases. The recurrence of symptoms often may be delayed for many years. It must be emphasized that in the 30 per cent of cases in which further trouble follows dilatation, the great majority of patients can be completely relieved of their symptoms by a second or third dilatation. In only about 2 of every 100 cases of cardiospasm does adequate dilatation prove unsuccessful, and operation is indicated in these cases.

In contrast, it is frequently assumed that operation, especially esophagogastrostomy, is uniformly followed by satisfactory results. This is not invariably true as may be seen by a review of the literature dealing with surgical treatment of cardiospasm. Recently, the writer had the opportunity of observing 3 patients within a period of one week who had undergone esophagogastrostomy for cardiospasm without any attempt having been made previously to dilate the cardia, and in all 3 cases the patients had not been relieved of their symptoms by operation. In 2 of these cases, subsequent dilatation by means of the Plummer hydrostatic dilator afforded complete relief of symptoms. In the third case further surgical treatment was necessary.

It is frequently mentioned, in discussing the advisability of surgical treatment for cardiospasm, that dilatation by means of the Plummer hydrostatic dilator carries with it a mortality rate of 2.8 per cent. Although this figure as stated by the writer in 1933\* was correct at that time, it is not correct today. It has been found that if a no. 60 F. sound is passed two days before hydrostatic dilatation is employed, it is possible to practically eliminate any risk from dilatation. Since the report published in 1933, approximately 2,000 patients with cardiospasm have been treated by hydrostatic dilatation without any mortality. In contrast to this figure, Ochsner and DeBakey,† in a report of 239 cases of cardiospasm collected from the literature in which cardioplasty and esophagoplasty had been performed, said that there had been 10 deaths or an operative mortality of 4.2 per cent. There is no doubt, however, with the improvements that have taken place in the field of thoracic surgery during the past few years, that this operative mortality can and will be appreciably lowered.

It is impossible to set down any hard and fast rules as to the most satisfactory method of treating cardiospasm in any given case as there are so many variable factors to be considered. Among these are: (1) the patient's reluctance to undergo dilatation because a certain amount of discomfort is associated with it, (2) the attending physician's acquaintance with the condition and ability to perform adequate dilatation of the esophagus, and (3) the skill of the surgeon who would undertake esophagogastronomy. The final solution of the problem will undoubtedly come with the eventual determination of the cause of the disease. Until such time, it would seem advisable to treat cardiospasm initially by conservative measures. When these fail or are impossible of accomplishment, operation is to be recommended.

HERMAN J. MOERSCH.

\* Moersch, H. J.: *Ann. Surg.*, **98**: 232, 1933.

† Ochsner, Alton, and DeBakey, Michael: *Laryngoscope*, **58**: 698, 1948.



## NOTE ON AN EARLY CASE OF GASTRIC FISTULA USED FOR PHYSIOLOGICAL STUDY

Recently\* Felix M. Cunha called attention to an interesting case of a fistula into the stomach observed by Benjamin Waterhouse when he was in Vienna in 1808. The case was reported by Professors Helm and Jakob in some medical journal of Vienna in 1803.

The patient was a woman of 58 years named Theresa Betz. After a good deal of suffering from borborygmus and pain in the epigastrium, a lesion of some kind worked its way out from the stomach and through the skin, producing a fistula. The woman was able to fish food out of her stomach with her fingers. She did this sometimes to relieve indigestion, or she would wash the stomach out and get help in this way. Helm noticed that milk introduced into the stomach curdled instantly. This coagulation could be hastened by first stimulating the inner surface of the stomach with a finger. Eggs and cheese were quickly digested, but not so soon as fresh meat; vegetables took longer.

There are a number of such cases scattered through the literature.

W. C. A.

\* Review of Gastroenterology, July, 1948.

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## Book Reviews

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THE MECHANISM OF ABDOMINAL PAIN. *V. J. Kinsella, M.B.* Angus and Robertson, Ltd. Sydney, Australia, 1948, pp. 230, price 32 shillings and sixpence.

This is an attractive book by a man who has evidently studied his subject well and long. He is able to write interestingly about it. His first chapter on the history and development of our present conception about the autonomic nervous system is excellent.

Opposite page 140 is a fine portrait of Sir Arthur Hurst, who is known to so many gastroenterologists.

On page 11, Kinsella states that some two hundred years before Meissner described his plexus, Willis had written about it.

On page 197, he speaks of paroxysmal proctalgia or a type of pain about the rectum which may be severe for about five minutes. This is probably due to spasm or cramp in the muscle of the prostate gland.

This is a thought-producing book and one which should be read by every thinking gastroenterologist.

Dr. Kinsella is greatly to be congratulated on writing a valuable monograph.

CLINICAL ROENTGENOLOGY OF THE DIGESTIVE TRACT. *Maurice Feldman, M.D.* The Williams & Wilkins Company. Third edition. Baltimore, 1948, pp. 901, price \$8.00.

This is a third edition of Feldman's fine book, which is well written and beautifully illustrated. It is full of information of great value to the gastroenterologist.

Dr. Feldman is to be congratulated on a good job well done.

MEDICAL RESEARCH IN FRANCE DURING THE WAR (1939-1945). Thirty articles gathered and presented by *Jean Hamburger, M.D.*, with a foreword by *Prof. Pasteur Vallery-Radot*. Editions Medicales Flammarion. pp. 306.

This volume prepared with the help of the Rockefeller Foundation, shows what some French investigators were able to do during the War, in spite of all their unhappiness and worry and depression and lack of food and fuel. There are several articles of interest to gastroenterologists, such as Gutmann's article on the Early Radiological Diagnosis of Cancer of the Stomach and Caroli's well illustrated article on the Radiomanometry of the Biliary Tract.

PEDIATRIC ANESTHESIA. *M. Digby Leigh, M.D., and M. Kathleen Belton, M.D.* The Macmillan Company. New York, 1948, pp. 240, price \$5.50.

Anesthesia has become such a highly technical and widely extended subject that now we have to have a book even on Anesthesia of Children. This is an attractive book and doubtless will be welcomed by anesthetists.

ÜBER NEUROME UND NEUROFIBROMATOSE, NACH UNTERSUCHUNGEN AM MENSCHLICHEN MAGENDARMSCHLAUCH. *F. Feyrter*. Verlag Wilhelm Maudrich. Vienna 1948. Imported by Grune & Stratton, Inc. New York, pp. 125, price \$3.50.

Feyrter is a pathologist who in the course of 1500 necropsies looked particularly for polypoid lesions projecting from the mucosa of the stomach and bowel. He has studied them histologically and has written up his observations in this monograph. In the 1200 patients who were over 45 years of age he found 53 of the little tumors. In 1600 necropsies on patients under 45 years of age he did not find any. The frequency of incidence increased with increasing age.

Histologically they were mostly fiber-rich tumors or what he called fibroma fibrillare. Others were fibroma fasciculare. Some apparently had developed on a chronic inflammatory basis. The fibromas tended to appear three times as often among women as in men. A few of the tumors were of the von Recklinghausen type.

Most of the little polyps arose from mesoderm. Some were rich in capillaries and some were made up largely of nerve fibers. They were found in the pars pylorica and never in the body of the stomach or the fundus. A number of the tumors contained many eosinophiles.

From the nature of these little polyps, one would not expect them to have produced any symptoms and Feyrter apparently did not go into this phase of the matter. Some of the tumors resembled gliomas. The book is of interest almost entirely to pathologists.

MANAGEMENT OF COMMON GASTRO-INTESTINAL DISEASES. Edited by *Thomas A. Johnson, et al.* J. B. Lippincott Company. Philadelphia, 1948, pp. 280.

As one would expect from the list of contributors to this little volume of essays on several gastro-intestinal topics, the book is an excellent one. Among the authors are Thomas A. Johnson, Burrill B. Crohn, Rudolf Schindler, Sara M. Jordan, Walter L. Palmer, Co Tui, Henry J. Tumen, Edward Weiss and A. H. Aaron. Among the topics discussed are chronic gastritis, the early recognition of gastric cancer, the diagnosis and medical management of benign gastric ulcer, the management of bleeding peptic ulcer, the present status of enterogastrone in the treatment of peptic ulcer, the hyperalimentation treatment of intractable peptic ulcers with hydrolysates, the psychosomatic aspects of gastrointestinal disorders, the present status of regional enteritis therapy, the diagnosis of pancreatic disease and cancer of the pancreas, cirrhosis of the liver, the diagnosis and management of viral hepatitis the diagnosis and management of ulcerative colitis, the diagnosis and treatment of irritable colon, carcinoma of the colon, the differential diagnosis and treatment of amebiasis and its complications.

The articles are all so good that it is hard to single out any for particular commendation. The article by Crohn and Yarnis on the Present Status of Treatment of Regional Enteritis is splendid. According to Crohn, Garlock who has now operated on over 150 patients with ileitis believes the best treatment is to close the bowel above the involved area of the ileum and then to make an anastomosis with the transverse colon. With this operation there has so far been recurrence in only 13.8

per cent. Primary or secondary resection carries with it a high mortality at a high recurrence rate.

Ivy and Grossman feel that the use of enterogastrone for the treatment of ulcers in man is hopeful.

Kirsner and Palmer in discussing the treatment of gastric ulcer wisely insist that if there is any doubt as to the nature of the lesion in the stomach the patient should be operated on. When one can be sure of the diagnosis it may be too late to work a cure.

The article by Weiss on the psychosomatic aspects of digestive troubles is good. As he says, it is extraordinary how little progress has been made in overcoming the tendency of physicians to diagnose only organic disease. He speaks of patients with "poly-surgical addiction" or a great fondness for being operated on.

On reviewing the histories of 1000 consecutive cases of irritable bowel syndrome, Collins and Van Ordstrand found that 302 operations had been performed uselessly of 204 of the patients. There is still need for a better recognition by physicians of the many functional and nervous disorders.

PSYCHIATRY FOR THE CURIOUS. *George H. Preston, M.D.* Reinhart & Company, Inc. New York and Toronto, 1940, eighth printing, pp. 148, price \$2.00.

This is an interesting and rather cleverly written little book. It was gotten out not for psychiatrists but for patients and the friends of patients. The author thinks with much justice that there has been too much mystery about psychoses, and that this does harm to the cause of psychiatry. He speaks first of what he calls Cheshire cat psychiatry because, as will be remembered, the Cheshire cat had a head but no body and eventually a grin without even a cat! As he says, the grin and the head and the body all belong together.

Preston says the psychiatrist believes that it is not so much the situations or the actual things that happen to people that are important as what people think and feel about what happens to them. The thesis in much of the book is that the psychopath is often a man who is trying, as best he can, to save himself from fear, disease, responsibility, blame, or hard work. He does this by doing certain things or by fleeing to certain refuges. Recurrent periods of excitement or depression may be vacations from reality. For instance, the man who drinks succeeds in this way in escaping from imagined or real criticism by society. Preston thinks that the most painful relations of the drunkard are with himself, and he uses alcohol in an effort to solve these troubles.

There is much that is suggestive in this volume but as usual, the reader wonders if the psychiatrist is right in spinning his pretty theories. The present-day symbolic explanations which psychiatrists give for every symptom are attractive to a person who likes this sort of thing, but the problem appears often to go deeper than that. Why is it that so many men who have failed in business or life, or have been disgraced, and who crave forgetfulness and peace and even death remain sane? They do not go into any refuge. And why on the other hand does a man or woman with a happy home, a good spouse, and everything to live for, suddenly go into a depres-

sion and just as suddenly, later, come out? As he or she may say, "the curtain came down," and later "it went up again." Someday we may find that a chemical poison produced the sudden change in the brain.

LA VIDA DEL ENFERMO Y SU INTERPRETACION ANAMNESIS. *Mariano J. Barilari and Leonardo Grasso*. El Ateneo. Buenos Aires, paper cover, pp. 305.

This is the largest monograph we have seen on the taking of histories. The writers are evidently of a philosophical turn of mind. At the beginning of each chapter there are a number of interesting quotations, which reveal the authors' trend of thought. For instance, on page 108, they quote from Sir James Mackenzie, who once complained that in our universities we tend to give the prizes to the man who remembers best. We don't try to find out whether he can think and reason, and we do not test him for these faculties which are the most useful ones that he can have during his life of medical practice.

On page 115 the writers call attention to a most useful way of studying medicine, and that is to look through the members of a large family to see if any of them have minor variants of the diseases which perhaps in one brother or sister is well marked and recognizable. For instance, one person may come in with a curious chronic jaundice, and a study of the other members of the family may show, in almost every one, some symptoms of blood destruction.

On page 150 is an interesting list of the most useful questions one can ask a person with the idea of finding out whether he or she is neurotic or psychotic.

# ABSTRACTS OF CURRENT LITERATURE

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## MOUTH AND ESOPHAGUS

FISHER, G. E. AND HICKS, J. J. The management of lye burns of the esophagus. *Southern Med. J.*, 41: 591 (July) 1948.

Detailed directions for the immediate treatment and subsequent management of patients with lye burns of the esophagus are given, and case reports are included. Patients who are seen several days after the ingestion of lye present a difficult problem, for they are usually dehydrated, feverish and have pain on swallowing. When seen in the acute stage, the patient is given a mouth wash of weak acetic acid and is asked to swallow a small amount of it. This is followed by a mouth wash and swallowing of a mild bland oil. A nasal tube is inserted into the stomach and the stomach is thoroughly washed with dilute acetic acid and water. A bland oil is instilled into the stomach through the tube. The patient is fed a high calorie, high vitamin diet through the tube daily, since the maintenance of good nutrition and the avoidance of secondary infection are all-important.

Dilatation is stressed, and to be successful it must be performed at regular intervals. On the fourth day an esophagoscopy is per-

formed, and the extent of mucosal damage determined. If only a small area of mucosa is involved, daily dilatations are performed using a mercury-filled bougie, the size of which depends upon the age of the patient. In the average case, 10-12 dilatations are usually sufficient. When the entire circumference of the esophagus is involved, dilatations with the E. N. Broyles dilator are performed daily.

ANTHONY M. KASICH.

## STOMACH

MAIMON, S. N., PALMER, W. L., AND KIRSNER, J. B. Prognosis in gastric cancer. *Am. J. Med.*, 5: 230 (Aug.) 1948.

The purpose of this paper is to report a further study of the factors responsible for prolonged survival in gastric carcinoma. Detailed postoperative follow-up on 93 cases of gastric cancer revealed that only 30 per cent survived 5 years or longer. The survival rate in males and females is about equal. Of the 5-year survivors, 50 per cent had symptoms of less than 1 year's duration. Patients with symptoms of over 2 years' duration had a relatively better prognosis than those with symptoms for less than

6 months before resection. Symptomatology disclosed upper abdominal digestive distress as the chief complaint. In some cases, the history suggested peptic ulcer; in others, there was pronounced anorexia and weight loss; in 3, the only complaints were weakness and fatigue. The 5-year survivors have no distinguishing symptoms as compared with the fatal cases.

Palpable epigastric tumors were noted in 26.6 per cent of cases, but large masses were not considered a contraindication to surgery. Other physical signs include a lemon-tinged skin, palpable liver and epigastric tenderness. The degree of anemia, the presence or absence of occult blood, and the level of gastric secretion was of little or no prognostic value, as was shown by 5-year survival data. The patients with polypoid lesions tended to be the most anemic.

The tumors resected from the 5-year survival group were, in most cases, sharply circumscribed and were of all types histologically. Metastases were present in 23 per cent, and there were no survivors in the Borrmann type IV group. Eighty per cent of the 5-year survivors were restored to useful life.

MICHAEL W. SHUTKIN.

CASBERG, M. A. AND MARTIN, W. P. Gastric diverticula. *Am. J. Surg.*, **76**: 172 (Aug.) 1948.

Gastric diverticula are admittedly uncommon and have been morphologically classified as true or false diverticula. Formation depends upon a site of lesser resistance due to an intrinsic mural weakness, extrinsic traction factors, and sometimes a combination of both. The cardiac region of the stomach is most frequently involved by gastric diverticula because of a muscle deficiency and an abundant penetration by large vessels. It has been observed more frequently in the later decades of life and has a higher incidence in females.

Histologically, the true diverticulum reveals all layers of the gastric wall while the false type shows a thinning out or absence of the muscular layer. Islands of pancreatic tissue, colon mucosa, benign and malignant tumors, have uncommonly been found in the sac. Acute perforation, frank diverticulitis, and strangulation have not been reported.

There is no specific pattern of symptomatology which will fit this clinical entity and the complaint of epigastric distress requires its consideration in the differential diagnosis. The diverticulum is usually asymptomatic and frequently a coincidental finding. Final diagnosis depends upon a roentgenographic study with follow-up observation for retention. Medical treatment should precede surgery and consist of postural drainage, small frequent feedings, and antispasmodics. Failure with this regimen plus psychiatric evaluation after 6 weeks, requires surgical consideration and resection. Two cases which underwent resection successfully are fully described and illustrated, and 6 case-history summaries are reported.

MICHAEL W. SHUTKIN.

## BOWEL

SNYDER, J. W. Chronic intestinal intussusception in the adult. *Southern Med. J.*, **41**: 586 (July) 1948.

Intussusception may occur anywhere in the alimentary tract from the stomach to the rectum. Invagination of the stomach into itself or into the duodenum has been described. The great majority of intussusceptions occur in the ileocecal region because of the failure of proper peritoneal fusion resulting in a freely movable segment consisting of the cecum, ascending colon and ileum. This condition is essentially an affection of infancy or childhood; from 80 to 87 per cent of the cases occur during the first 2 years of life. In most cases there is no obvious etiology, although occasionally Meckel's diverticulum, intestinal polyps, lymphoma, or other tumors are seen and may be the causative factor.

The author describes the signs and symptoms of the condition. There is a detailed report of one case.

ANTHONY M. KASICH.

BARGEN, J. A. Evaluation of the newer therapy of ulcerative colitis. *Southern Med. J.*, **41**: 646 (July) 1948.

Before treatment of ulcerative colitis can be undertaken, a clear concept of the type of disease present is of extreme importance. The author divides ulcerative colitis into eleven types: 1) "streptococcic type"—the

most common, in which the rectum presents a granular, edematous, friable mucous membrane, bleeding at the slightest touch; 2) the type in which various segments of the colon are involved together with the rectum; 3) segmental or regional type, in which segments of the bowel from the cecum to the sigmoid are involved; 4) tuberculous colitis; 5) the type occasionally seen after bacillary dysentery; 6) amebic colitis; 7) the type due to virus of lymphopathia venereum; 8) allergic colitis. 9) the type due to deficiency states, other than sprue or pellagra; 10) sarcoidosis, in which hyperplastic noncaseous lesions and ulceration occur; and 11) staphylococcal type of ulcerative colitis.

The author gives an outline of the steps necessary to establish the diagnosis and discusses treatment of the streptococcal type in detail. Aside from the usually prescribed bedrest, diet, local measures to relieve anal discomfort, and supportive therapy, the use of sulfonamides and thyroid depressing drugs is discussed. Favorable results in some cases have followed the use of thiouracil. Finally, the similarity of ulcerative colitis and rheumatic fever is noted. A new drug, "salazopyrin", a combination of salicylate and sulfapyridine which the author has used in 8 cases with success, is recommended as worthy of trial.

ANTHONY M. KASICH.

BARGEN, J. A. The present-day therapy of thrombo-ulcerative (streptococcal) colitis. *Med. Clinics N. Am.*, 967 (July) 1948.

Medical measures are indicated in uncomplicated cases of thrombo-ulcerative colitis. Rest is indicated in the acute fulminating case but in the chronic case it should be replaced by restful recreation. Interesting diversion distracts the attention of the patient from his need of remaining near a toilet. The use of diet, vitamins, nursing care, oxygen, transfusions, parenteral fluids and removal of foci of infection are discussed. The use of irrigation is discouraged but various preparations are instilled into the rectum when the disease is confined to the rectum and sigmoid. The author continues to use autogenous vaccine in the mild cases. Courses of sulfonamides in the form of neoprontosil and sulfathalidine are given. A new combination of sulfonamide and salicyl-

ate called salazopyrin, compounded because of the similarity between thrombo-ulcerative colitis and rheumatic fever, has given gratifying results. The acute fulminating phase may respond to sulfadiazine or penicillin. The results from streptomycin have not been encouraging.

Surgical management of the acute fulminating case is accompanied by a high mortality. Intractability is not considered an indication for ileostomy. Surgery should be reserved for the late sequelae as polyps, neoplasms, strictures, perianal fistulas, localized perforations and abscesses.

S. G. MEYERS.

DEVINE, H. AND DEVINE, J. Subtotal colectomy and colectomy in ulcerative colitis. *Brit. Med. J.*, 4567: 127 (July) 1948.

The authors describe 11 patients, seriously ill with ulcerative colitis, for which a policy of "careful radical surgery" was planned. There were 2 deaths; one caused by an adynamic ileus immediately following the first-stage modified enterostomy, and one, 3 months after the first stage, due to tissue deficiency and toxemia. Six patients survived subtotal colectomy; one, a subtotal colectomy combined with excision of the rectum; one, a partial colectomy involving two-thirds of the colon; and one, the first stage of colectomy. Six patients are regarded as cured; they have no bowel discomfort and live normal lives. Removal of the colon is considered the treatment of choice when ulceration and loss of substance of the mucosa has taken place and the medical treatment is not effective.

JOSEPH B. KIRSNER.

POTH, E. J. Bowel healing as influenced by intestinal antiseptics. *Southern Med. J.*, 41: 672 (Aug.) 1948.

The accumulated clinical experience of numerous observers during the past 6 years has repeatedly stressed the value of sulfasuxidine and sulfathalidine as adjuvants in intestinal surgery. When these agents are used properly in the preoperative preparation and postoperative care of patients, operations can be performed with safety on the open viscus without fear of peritonitis or severe wound infection.



The author reports the results of experiments in which he was able to demonstrate that animals whose colons were operated upon after administration of sulfa drugs had smoother postoperative courses. There was minimal edema of the mucosa in treated animals, and the slight inflammation which did occur subsided rapidly with limited lymphocytic infiltration, rapid revascularization and orderly fibroplasia. In the untreated animals, on the other hand, wound infection, peritonitis, stitch abscesses and local soft tissue infections were the usual findings.

ANTHONY M. KASICH.

EVANS, W. A., JR. Obstructions of the alimentary tract in infancy. *Radiol.*, **51**: 23 (July) 1948.

The distribution of the more common obstructing or potentially obstructing lesions, observed in 400 infants during the past 7 years at Children's Hospital of Michigan, is the following: Hypertrophic stenosis of the pylorus — 50 per cent, intussusception — 20 per cent, atresias of the esophagus — 4 per cent, atresias of the duodenum — 2 per cent, atresias of the jejunum-ileum — 3 per cent, atresias of the colon-rectum — 2 per cent, atresias of the anus — 5 per cent, strangulated hernia — 8 per cent, meconium ileus — 2 per cent, congenital bands — 2 per cent, volvulus — 2 per cent. The age of the patient is often an important consideration in pediatric diagnosis, and this is particularly so in alimentary tract lesions. The atresias, meconium ileus, and most of the cases of volvulus are seen during the first days of life. Hypertrophic pyloric stenosis usually occurs between 3 and 10 weeks of age. It will be noted that there is little overlapping of these 3 groups. Meconium ileus is difficult to differentiate from ileal atresia. However, if there is no abrupt termination of the gas-distended bowel, and if there is a mottled appearance of the meconium and a very small caliber of the colon, meconium ileus may be recognized.

FRANZ J. LUST.

LEROYER, C. P., JR. AND WHITE, B. V. Diagnostic and therapeutic problems in diverticulitis. *New Eng. J. Med.*, **239**: 245 (Aug.) 1948.

The clinical features of 200 cases of diverticulitis treated at the Hartford Hospital between 1927 and 1946 are reviewed. The relative incidence of the leading symptoms and signs was essentially similar to those generally reported. A notable exception was the occurrence of pain in the lower back as a prominent feature in 20.5 per cent of the cases. A finding in accord with other authors' experiences, but worthy of special emphasis, was the presence of melena in 16.5 per cent. Diagnostic confusion occurred most frequently in cases that presented signs suggestive of acute appendicitis. There was also difficulty in clinical differentiation between masses in the lower abdomen or pelvis, on one hand, and carcinoma of the bowel or genitourinary lesions, such as ruptured ovarian cyst and carcinoma of the seminal vesicles or prostate, on the other.

Complications were encountered in 50 cases (25%). These included 7 instances of obstruction secondary to ligneous induration of the affected sigmoid, and 43 perforations. Thirty-two of the latter led to local abscesses, 6 to fistulas, 4 to mechanical obstruction, and only 1 to generalized peritonitis.

ANTHONY M. KASICH.

MIGLIACCIO, A. V. AND BEGG, C. Meckel's diverticulum. *Am. J. Surg.*, **76**: 188 (Aug.) 1948.

This review covers the experience with Meckel's diverticulum and its complications over a 12-year period. This embryological defect is a true diverticulum of the small bowel derived from the omphalomesenteric duct. It is more common in males, varies in size and location along the ileum, and is found in 1-2½ per cent of patients coming to autopsy. It occurred most frequently in the first two decades of life, and was responsible for symptoms in 42 per cent, in a series of 50 cases. The authors' revised classification comprises the following groups: (1) obstructive, (2) diverticulitis, (3) heterotopic, (4) umbilical, (5) tumor, and (6) incidental.

Specific diagnostic criteria for Meckel's diverticulum are lacking and the diagnosis is rarely made preoperatively. Symptoms are as varied as the complications and are,

in fact, the symptoms of the complications. In children, peptic ulceration of Meckel's diverticulum is an important cause of intestinal bleeding, and this diagnosis should be considered in every case. Roentgenography is of limited value diagnostically even though barium retention has been observed in the sac occasionally. The treatment of choice is wide resection in an effort to remove all heterotopic tissue. Diligent pre- and post-operative search for Meckel's diverticulum, especially in children, will reveal a greater incidence than has hitherto been recorded.

MICHAEL W. SHUTKIN.

### LIVER AND GALL BLADDER

SNAPE, W. J., FRIEDMAN, M. H. F., and SWENSON, P. C. Correlation between the cholecystogram and the secretin test for gall bladder function. *Am. J. Med. Sci.*, **216**: 188 (Aug.) 1948.

Pancreatic secretin having a choleretic effect but free of a cholecystokinetic effect was used in 64 patients as a measure of gallbladder function. Secretin prepared by the procedure of Friedman and Thomas was given intravenously to fasting subjects. Through a double lumen tube, samples of gastric and duodenal contents were collected at intervals for an hour subsequent to giving secretin. Bile pigment concentration was determined on these specimens. When there was a functioning gall bladder most of the bile formed during the test was stored there and little pigment appeared in the duodenum. When the gallbladder was not functioning, bile flowed into the intestine giving a juice with a high color index.

The authors found a fair degree of correlation between the secretin test and cholecystography in both normal and diseased subjects. The former is suggested as a useful testing procedure when data from the cholecystogram are difficult to interpret.

LEMUEL C. MCGEE.

BACHHUBER, C. A. AND GILBERT, A. E.

Four hundred consecutive cases of jaundice. *Am. J. Surg.*, **76**: 144 (Aug.) 1948. In the presence of jaundice, daily observation of stool color and the urine will readily reveal the type of jaundice involved. The

persistence of an acholic stool is significant of obstructive jaundice, be it intra- or extra-hepatic. In this review 400 consecutive records of jaundice were studied and analyzed.

There is an over-all mortality rate in jaundice of about 65 per cent. The inflammatory group, including those with catarrhal jaundice, offers the best opportunity for recovery, while patients with malignancy have a 100 per cent mortality. The two groups, carcinoma of the head of the pancreas and common duct stones, are responsible for one-half of the jaundiced patients. Malignancy, neither primary nor secondary, will produce jaundice without pressure on the intra- or extra-hepatic ducts. Surgery in this group is as yet very disappointing.

Catarrhal jaundice is readily diagnosed and responds to conservative medical therapy. In cases with common duct stones and inflammation, relief and cure is possible. Surgery is at its best in cholangitis, where results are good and mortality low. In jaundice of toxic and hemolytic origin, a high percentage can be given medical or surgical relief or cure. In jaundice due to portal cirrhosis, the outlook is poor and most cases will terminate fatally. Finally, the cases with acquired stricture and jaundice present a rather hopeless prognosis.

MICHAEL W. SHUTKIN.

AMSTERDAM, G. H. AND STERLING, J. A.

Conservative therapy of residual calculi following operations on the common bile duct. *Ann. Surg.*, **128**: 30 (July) 1948.

Two cases are reported to demonstrate the end-results of conservative therapy for residual calculi following surgery of the biliary tract.

A 38-year old white male had common duct obstruction due to a calculus remaining therein after cholecystectomy. Through a "T" tube which had been left in place he received daily instillations of 3 to 4 cc. of ether into the common duct. Eight weeks later all evidence of obstruction had disappeared and in another month the "T" tube was removed. There have been no further complaints referable to the biliary tract during an 18 months follow-up.

A white female of 54 years similarly had a

radiotranslucent shadow in the terminal portion of the common duct (shown by a cholangiogram) following surgery. Ether was injected daily for several weeks and then 2 to 4 times weekly for 5 months. The shadow resembling a stone in the papillary area of the common bile duct persisted. After re-admission to the hospital there was lavage of the duct using novacaine solutions under increasing intraductal pressure. After several months of freedom from symptoms a cholangiogram showed no evidence of calculi and the "T" tube was removed nearly one year after its insertion. The patient had no symptoms during a subsequent year of observation.

LEMUEL C. MCGEE.

MARION, D. F. AND RUMBALL, J. M. The practical value of liver function tests in clinical medicine. *Southern Med. J.*, **41**: 601 (July) 1948.

Sixty-six patients with liver disease were selected for studies by means of liver function tests. These tests were: icteric index, thymol turbidity, cephalin flocculation, bromsulfalein retention, serum phosphatase and urinary urobilinogen determinations. They were selected because of their relative simplicity. This paper includes case reports and 11 charts showing graphically the variations produced in these tests by various liver diseases. The authors conclude that the 6 tests under discussion are sufficient for routine everyday use, and that they aid immeasurably in making more accurate diagnoses and assist in the formulation of more practical and successful treatment. These tests, furthermore, are not beyond the scope of the average small hospital and private clinical laboratory.

ANTHONY M. KASICH.

TERRY, L. L. AND BOZICEVICH, J. The importance of the complement fixation test in amebic hepatitis and liver abscess. *Southern Med. J.*, **41**: 691 (Aug.) 1948.

Because of the frequent difficulty in identification of *E. histolytica* even by experts, there is a great need for a simple test for amebiasis. In the authors' experience based upon intensive study of 15 cases, the com-

plement fixation test is of great importance in such diagnosis, especially when the result is positive. The test is not to be considered pathognomonic of liver involvement, however. Nevertheless, if the clinical picture is consistent with amebic hepatitis or abscess, the complement fixation test is far more reliable than a history of diarrhea, stool findings, or proctoscopic examination.

The authors discuss the complement fixation test in detail and give the results of its application in 15 cases. Ten cases showed positive complement fixation tests on the initial and all other tests prior to therapy. Three cases gave a negative reaction on the initial test. However, two of these sera showed a positive reaction when retested with a potent antigen; the other remained negative. No definitely false positive reactions were obtained. The duration of the antibody titer after adequate therapy in amebic involvement of the liver is uncertain. The conclusion is drawn that while these observations are incomplete, the serological test may have prognostic as well as diagnostic value.

ANTHONY M. KASICH.

MIRICK, G. S. Hepatitis, modern concepts. *Southern Med. J.*, **41**: 743 (Aug.) 1948.

It has been stated that infectious hepatitis and homologous serum jaundice are different because of apparent differences in the incubation period, clinical picture, age susceptibility, distribution of the virus in the body, immunity, and the appearance of secondary cases. The author discusses the two forms of hepatitis under these headings, and concludes that these differences are open to question. There is doubt whether there are any real differences between homologous serum jaundice and infectious hepatitis other than the fortuitous difference of the mode of transmission. It is concluded that while antigenically different strains of virus may occur, and while strains showing some difference in the incubation period are noted, the artificial division of the disease into 2 types may be arbitrary and not founded on clinical, pathological, or epidemiological facts.

ANTHONY M. KASICH.

## PANCREAS

REEVES, R. J. AND MORAN, F. T. Diffuse pancreatic calcification. An analysis of six cases. *Radiol.*, **51**: 219 (Aug.) 1948. The authors describe the case of a 4-year old child with diffuse pancreatic calcification, apparently the youngest case on record. Five other cases, all under 35 years of age, are also reported; these patients had severe complaints for 2 to 8 years. The child had never had abdominal pains. Two patients gave a history of excessive alcohol consumption. Four cases had diabetes mellitus. Serum amylase was increased in one case. The roentgenologic finding of calcium within the pancreatic parenchyma is of considerable significance. Since it becomes deposited in areas of fat necrosis, fibrosis, or degenerative tissue, it indicates the site of a pathologic process. Two cases had pancreatic achylia. Due to the pains, one patient bordered on drug addiction; another had such intractable pains that bilateral ganglionectomy had to be performed.

FRANZ J. LUST.

GOIN, L. S. Fibrocystic disease of the pancreas. *Radiol.*, **51**: 36 (July) 1948.

Fibrocystic pancreatic disease is a congenital, familial, highly fatal disease of infants, and is regularly accompanied by pulmonary changes which are demonstrable in the roentgenogram. The disease has become recognized as a clinical entity only in the past 10 years due almost entirely to the work of Dorothy Andersen. The cause of the disease remains unknown. The histopathologic factor is that of obstruction of the smaller pancreatic ducts and subsequent dilatation of the acini. There is a vitamin A deficiency. Among the significant lung changes seen roentgenographically are bilateral hilar densities with mottled linear densities extending outward, marking a sort of aura about the cardio-vascular shadow. Bronchopneumonic patches are seen, and a honeycomb appearance of the lung bases frequently represents bronchiectasis. The bronchopneumonic areas may be quite extensive, and bronchopneumonia is commonly the immediate cause of death. The

symptoms and clinical findings are those of gross deficiency of pancreatic secretion. The stools are bulky, foul, and gray; the abdomen is distended. The fat content of the stools is 60 per cent. There is delayed glucose absorption and poor vitamin A absorption. Diarrhea and repeated respiratory infections develop. Vitamin A up to 150,000 units per week and casein hydrolyzates instead of milk should be given.

FRANZ J. LUST.

NOTHMAN, M. M., PRATT, T. D., AND BENNOTTI, J. The effect of the ligation of the pancreatic ducts and of pancreatectomy after duct ligation on serum lipase. *J. Lab. Clin. Med.*, **33**: 833 (July) 1948.

The serum lipase in 26 dogs rose after ligation and division of the pancreatic ducts. The values dropped immediately after the operation in 3 dogs, on which total pancreatectomy was performed without previous ligation, and in another 5, on which this operation was performed after ligation and division of the ducts. Two dogs survived the second type of operation for over a month; both of these had, at the end of 3 weeks, serum lipase values higher than they had before operation.

The authors claim that the pancreatic origin of serum lipase is proved by its rise after ligation and division of the pancreatic ducts and by the decrease after total pancreatectomy, especially in those dogs in whom ligation previously had produced a rise. They regard the recurrence of a higher serum lipase 2 to 3 weeks after total pancreatectomy as proof that there also exists an extrapancreatic source for the enzyme.

EDGAR WAYBURN.

POPPER, H. L., NECHELES, H., AND RUSSELL, K. C. Transition of pancreatic edema into pancreatic necrosis. *Surg. Gyn. Obs.*, **86**: 79 (July) 1948.

Animal experimental work by the authors has proven that there is a transition of pancreatic edema into pancreatic necrosis by temporary occlusion of the main pancreatic (gastroduodenal) artery. The authors point out the importance of the arterial blood supply of the pancreas, since its interruption

may cause changes that range from mild forms of necrosis to severe hemorrhage and necrotizing pancreatitis.

FRANCIS D. MURPHY.

WAPSHAW, H. The blood diastase and lipase changes in acute pancreatitis. *Brit. Med. J.*, **4566**: 68 (July) 1948.

The changes in blood diastase and lipase in 10 cases of acute pancreatitis are reported. It was found that these enzyme determinations were equally satisfactory as indicators of acute pancreatitis. Their clinical application seems to be limited to the initial stages of the disease owing to the nature of the specific enzyme reaction. Evidence is given to show that serial diastase estimations may furnish information regarding the grade of severity of the disease.

JOSEPH B. KIRSNER.

### ANEMIAS

CLARK, G. W. A survey of the treatment of pernicious anemia in relapse. *Am. J. Med. Sci.*, **216**: 71 (July) 1948.

The response of 80 pernicious anemia patients in relapse treated by liver extract is compared to that of 73 patients treated by folic acid. Treatment over a 30-day period showed an average difference in hemopoietic response of 0.6 million erythrocytes in favor of those treated by liver extract. There are extreme variations in the reticulocyte response, produced by the same therapy in different patients having essentially the same initial erythrocyte level. The reticulocyte response is an unreliable measure of the potency of anti-anemia preparations. Certain revisions are suggested for U.S.P. "standards" in evaluating the potency of anti-anemia preparations.

LEMUEL C. MCGEE.

STEVENS, J. E. AND HALL, B. E. Present-day concepts of therapy in pernicious anemia: A review. *Med. Clinics N. Am.*, **1113** (July) 1948.

*Lactobacillus casei* factor, vitamin M, vitamin B<sub>6</sub>, and possibly Wills factor are related and might even be identical, being composed of pteroylglutamic acid (folic acid). The acid or its conjugate is found in varying amounts in food; foods rich in folic acid are

liver, kidney, and fresh green vegetables as spinach and cauliflower. After ingestion of foods, the cleavage of the conjugated forms of folic acid by the enzyme, conjugase, may be limited by the presence of a substance called "conjugase inhibitor". Patients with pernicious anemia in relapse do not properly utilize the naturally occurring folic acid conjugate found in foods; when remissions are induced they are capable of liberating free folic acid from conjugates and using it to stimulate megaloblastic maturation in the bone marrow.

Folic acid has not been as efficacious in the therapy of pernicious anemia as originally claimed. The development of neurologic relapses in patients, maintained in a state of hematologic remission, demonstrates the risk of using folic acid. Recent reports indicate that folic acid may not only allow neurologic relapse to occur but indeed may precipitate it. Liver extract is the safest agent for routine treatment.

S. G. MEYERS.

### PROCTOLOGY

MUIR, E. G. Rectal cancer and preservation of function. *Brit. Med. J.*, **4570**: 286 (Aug.) 1948.

The author reviews the surgical treatment of rectal cancer with respect to the preservation of normal defecation. He concludes that there is a sound basis for operations which aim at preserving a functioning anus in high rectal and recto-sigmoid growths. However, even in early cases and with adequate excision, carcinoma can reappear at the anastomatic site. To be certain of continence the ano-rectal ring must be preserved. Of the various methods, abdominal resection with anastomosis, and "pull-through" resection appear preferable. A preliminary transverse colostomy lessens the risk and dangers of infection. The use of sulfonamides and penicillin has reduced the mortality of all methods of rectal resection to a low figure.

JOSEPH B. KIRSNER.

### ULCER

CRAIG, J. D. The evolution of gastric and duodenal ulceration. *Brit. Med. J.*, **4571**: 330 (Aug.) 1948.

Alterations in the incidence, age and sex distribution, and clinical features of gastric and duodenal ulcer were analyzed over a period of years on the basis of clinical surveys, the Registrar-General's returns, and post-mortem statistics. The data indicate a considerable increase in the incidence of duodenal and gastric ulcer in males since the beginning of the nineteenth century. In females, the incidence of gastric ulcer has diminished markedly, whereas that of duodenal ulcer has risen. Increased mortality from gastric and duodenal ulcer in males and from duodenal ulcer in females has occurred principally in the later age groups, although even among the younger patients, the mortality has either risen or remained steady. The various forms of peptic ulceration, gastric and duodenal, acute and chronic, are regarded, from the etiological point of view, as separate though related conditions. Further emphasis is given to the view that the evolution of gastric and, more particularly, duodenal ulceration has paralleled the steadily increasing tempo of modern civilization.

JOSEPH B. KIRSNER.

McELHINNEY, W. T. AND HOLZER, C. E., JR. Factors influencing mortality from acute perforated peptic ulcers. *Surg. Gyn. Obs.*, 86: 85 (July) 1948.

This study is made up of 336 cases of acute perforated peptic ulcer seen at the Cincinnati General Hospital from 1935 to 1946. The operative mortality rate of these patients has been reduced from 21 per cent to 10.7 per cent in this 12-year period. In the patients undergoing operation within the first 6 hours after perforation, the most striking results were obtained when the patient was given chemotherapy. No deaths occurred in this group. In those patients operated within 7-12 hours and given chemotherapy, mortality was reduced from 21.6 per cent to 10 per cent with the use of sulfonamides, and to 7.7 per cent with the introduction of penicillin. Perforated ulcers of over 24-hours' duration did very poorly.

The authors feel that, since peritonitis was the cause of death in these cases 3 times as often as any other cause, the bacterial

element in perforated ulcer is an important factor to be considered.

FRANCIS D. MURPHY.

STEIN, I. F., JR. AND MEYER, K. A. Studies on vagotomy in the treatment of peptic ulcer. III. Physiological aspect. *Surg. Gyn. Obs.*, 86: 188 (Aug.) 1948.

This report is concerned primarily with the changes in gastric function following vagotomy in 30 patients. The following determinations were made on a significant number of patients: 12-hour night secretion, basal secretion, the effect of histamine and caffeine on gastric secretion, the effect of atropine on basal secretion, the spontaneous motility of the stomach, the effect of insulin on gastric secretion and motility, the pain threshold to electrical stimulation, and the production of pain by the introduction of acid into the stomach.

It was found that there is marked diminution of night secretion and basal secretion following complete vagotomy and that the secretory response of the stomach to caffeine and histamine is greatly reduced. It was also found that increased gastric secretion and motility produced by insulin hypoglycemia is abolished after vagotomy.

While the vagi are the sole mediator of the cephalic phase of gastric secretion, they are also concerned in the interdigestive and gastric period. Complete vagotomy is followed by immediate relief of ulcer symptoms, but this does not prove excessive vagal activity causes peptic ulcer. In some way complete vagotomy interrupts a mechanism necessary for chronicity of peptic ulceration.

FRANCIS D. MURPHY.

ST. JOHN, F. B., HARVEY, H. D., FERRER, J. M., AND SENGSTAKEN, R. W. Results following subtotal gastrectomy for duodenal and gastric ulcer. *Ann. Surg.*, 128: 3 (July) 1948.

The authors review the experience of a teaching hospital with gastric resection for peptic ulcer. Whereas the surgical mortality rate was 20 per cent three decades ago and 12 per cent two decades ago, it fell to 4.6 per cent for the period, 1936-1945. During this last period, 394 partial gastric resections were performed for peptic ulcer. Success-

ful follow-up was obtained in 344 (87.3%) of the patients. Thirty-seven (10.7%) of those followed were classed, on the basis of symptoms, as unsatisfactory results. No patient whose course was considered satisfactory for 5 years following operation, fell thereafter into the unsatisfactory group. Jejunal (marginal) ulcer was proved in but 2 of the cases surviving operation, but was suspected in 3 others because of symptoms.

Of the 18 postoperative deaths, 16 occurred in patients over the age of 45 years, 13 in patients over the age of 50 years. Inasmuch as 184 patients were 45 years of age or under, resection is considered to be a relatively safe procedure for the younger age group. On the other hand the mortality for patients above 45 years was 7.8 per cent. In view of these findings "it is most difficult to dictate the form of therapy that should be used" in the older people whose ulcer is in the duodenum.

LEMUEL C. MCGEE.

OWENS, F. M., JR. The problem of peptic ulcer following pancreatectomy. *Ann. Surg.*, 128: 15 (July) 1948.

Owens describes 3 patients who developed peptic ulcer in the stomach or jejunum subsequent to the necessary removal of all or part of the pancreas. In each instance the biliary tract had been anastomosed to the bowel distal to the gastroenterostomy. Such a repair of the bowel continuity deprives the patient of the maximal neutralizing effect of the bile and is comparable in its effect to the Mann-Williamson operation for the experimental production of ulcer in dogs. Surgical technics which allow bile (and pancreatic juice in partial pancreatectomy) to pass the gastrojejunal stoma are described and recommended as preferable for such patients.

LEMUEL C. MCGEE.

SCHILLING, J. A. AND PEARSE, H. E. Re-evaluation of the role of the pyloric antrum in marginal peptic ulcers. *Surg. Gyn. Obs.*, 86: 225 (Aug.) 1948.

An experimental study is described in which two groups of 10 dogs were used. A subtotal gastrectomy was performed in each dog, with removal of approximately two-

thirds of the stomach. An anterior type of gastrojejunostomy was performed, but in the first group of animals the pyloric antrum was excluded and left intact, and in the second group the pylorus was resected. The experimental results were as follows: In the first series, 9 of the 10 dogs developed marginal jejunal ulcers; in the second group of 10, only 2 developed ulcers. The authors feel that the pyloric antrum definitely contributes to the increased incidence of marginal peptic ulceration and conclude that the pyloric antrum should always be removed at operation.

FRANCIS D. MURPHY.

WENER, J. AND HOFF, H. E. The neuro-humoral aspects of peptic ulcer formation.

*Can. Med. Assoc. J.*, 59: 115 (Aug.) 1948. The authors review extensively the evidence for the neurogenic concept of ulcer formation and conclude that two distinct, but closely related processes must be considered: that which initiates the ulcers, and that which is responsible for the progression of these lesions to the chronic form. Although it has been clearly demonstrated that vascular alteration, leading to local tissue anoxemia and necrosis, is the most important factor in the initiation of erosion and ulcers, the lesions produced have rarely, if ever, gone on to chronicity. The repeated vascular insults induced in various ways, although severe, have been relatively transitory in nature. Thus far, it has not been possible to reproduce sustained reflex disturbances in dogs, comparable to those suspected to occur in man due to long-lasting emotional conflicts. The authors further state that although erosions or acute ulcers occur frequently in man, comparatively few people develop chronic peptic ulcer. Most of these lesions heal rapidly. It has also been shown that chronic peptic ulcers heal as rapidly as the acute ulcers, when the state of sustained emotional conflicts is removed. These observations are interpreted to offer a physiological basis for the neurogenic concept of ulcer formation and to re-emphasize the importance of marked circulatory disturbances in the initiation of acute gastrointestinal lesions, ranging from mucosal hemorrhages to erosions and ulcers.

JOSEPH B. KIRSNER.

## PHYSIOLOGY: SECRETION

FERRER, J. M., JR. The effect of tetra-ethyl ammonium chloride on gastric secretion and acidity in peptic ulcer. *Surg. Gyn. Obs.*, **86**: 76 (July) 1948.

Sixteen patients with peptic ulcer were studied to determine whether the excessive night secretion could be prevented by vagus nerve block with tetra-ethyl ammonium chloride (Etamon). Effective reduction of the night secretion or acidity or both was accomplished in 12 out of 17 gastric drainage tests done after the intramuscular injection of 20 mg. of Etamon per kilogram of body weight, if repeated at 4-hour intervals.

FRANCIS D. MURPHY.

HARTMAN, S. A. AND MOORE, D. M. The effect of tripeleminamine hydrochloride (pyribenzamine) on the gastric acidity of patients with peptic ulcer. *Am. J. Dig. Dis.*, **15**: 271 (Aug.) 1948.

Because of the antihistaminic effect of pyribenzamine, an attempt was made to study the influence of this drug on gastric acid secretion in patients with peptic ulcer. Pyribenzamine was given in doses of 100 mg. three to four times daily. Charts of 4 patients are reproduced indicating that the administration of pyribenzamine had no significant effect on the volume or the degree of acidity of the gastric juice in these patients. Benadryl, in a dose of 300-400 mg. daily, was likewise found to have no effect on the gastric acidity of 2 patients with duodenal ulcers.

HENRY TUMEN.

WOODWARD, E. R., BIGELOW, R. R., AND DRAGSTEDT, L. R. Quantitative study of effect of antrum resection on gastric secretion in Pavlov pouch dogs. *Proc. Soc. Exp. Biol. Med.*, **68**: 473 (July-Aug.) 1948.

Previous work on Edkins' gastrin for the most part has been qualitative rather than quantitative. For this reason, the chemical phase of gastric secretion was studied, using the quantitative methods of Dragstedt, Haymond, and Ellis. Large Pavlov pouches were used. The 24-hour pouch secretion was collected, and volume, free acidity, and hydrochloric acid content determined. After a period of observation, the entire antrum

was resected and, following recovery, comparable data collected.

In all animals, antrum resection resulted in a pronounced reduction in pouch secretion. The average reduction in the 24-hour volume was 73 per cent, and in free acidity 57 per cent. The average reduction in 24-hour hydrochloric acid output was 84 per cent. These data indicate that the antrum is important in the chemical or hormonal phase of gastric secretion, and supports Edkins' hypothesis.

H. NECHELES.

GROSSMAN, M. I. AND ROBERTSON, C. R. Stimulation of gastric secretion by urticariogenic wetting agent (Tween 20) and its inhibition by benadryl. *Proc. Soc. Exp. Biol. Med.*, **68**: 550 (July-Aug.) 1948.

It is known that, when whealing of the skin is produced in the human being, gastric acid secretion is stimulated. The interpretation is that the skin releases histamine or a histamine-like substance (H-substance); some of it is carried into the general circulation where it produces effects similar to those produced by the injection of histamine, including stimulation of acid secretion by the stomach.

Tween 20 produces urticaria and stimulates gastric secretion when injected intravenously in a dose of 0.8 mg./kg. in dogs with gastric pouches. Pretreatment with benadryl prevents or reduces the urticariogenic and secretory effects of this wetting agent in most instances. Since benadryl does not inhibit histamine-stimulated gastric secretion, its mode of action in counteracting Tween 20-stimulated secretion must involve another mechanism.

H. NECHELES.

WOOD, D. R. Caffeine and gastric secretion. *Brit. Med. J.*, **4570**: 283 (Aug.) 1948.

Cats were prepared for continuous drainage of gastric juice by ligating the cardia and duodenum and inserting a cannula into the stomach through the pylorus. Histamine acid phosphate was injected subcutaneously in a dose of about 0.18 mg. per kg. of body weight, and the secretory response measured. Solutions of 1 or 2 per cent of caffeine sodium benzoate, theobromine sodium sal-



icylate, and theophylline sodium acetate were then slowly injected intravenously over a period of 2-5 minutes followed by a second dose of histamine. The data indicate that caffeine, given in a dose which does not usually stimulate gastric secretion in the anesthetized cat, consistently potentiates the gastric stimulant action of histamine. A similar but less consistent effect was observed after theobromine and after theophylline. It is suggested, on the basis of these experiments, that ulcer patients should restrict their intake of beverages containing caffeine and should limit their consumption of foods and drinks containing theobromine and theophylline.

JOSEPH B. KIRSNER.

#### PHYSIOLOGY: ABSORPTION

JONES, C. M., CULVER, P. J., DRUMMEY, G. D., AND RYAN, A. E. Modification of fat absorption in the digestive tract by the use of an emulsifying agent. *Ann. Int. Med.*, **29**: 1 (July) 1948.

Numerous pathological states interfere with intestinal absorption of fat such as reduction of the area of absorbing surface due to a chronic inflammation of the small intestine, entero-anastomosis with short circuit, pancreatic fibrosis, and subtotal gastrectomy. In all these conditions there may be an excessive loss of fat in the stools. The authors have investigated the use of a wetting or emulsifying agent to lower the surface tension of the dietary fat and reduce the size of the fat globules, thereby increasing the total surface area of the lipoid material presented to the intestinal villi. The substance polyoxyethylene sorbitan monooleate

("PSM"), sold under the trade name of "Tween 80" was studied. No toxic manifestations were noted in animals, or in man in doses of 15 grams daily. Increased fat absorption was demonstrated by reduction of fecal fat, vitamin A tolerance curves, and weight gain in patients on a stabilized regime. The drug promises to be of benefit in conditions of serious malnutrition secondary to celiac disease, sprue, regional ileitis, etc.

S. G. MEYERS.

#### MISCELLANEOUS

BROWN, R. B. AND ANDRUS, D. L. Penicillin in the postoperative treatment of peptic ulcer with perforation and appendicitis with perforation. *Ann. Surg.*, **128**: 57 (July) 1948.

During a recent period of 18 months, there were 42 cases of perforated peptic ulcer and 97 cases of perforated appendix operated on at the Philadelphia Naval Hospital. Two patients with perforated ulcer died, a mortality of 4.8 per cent. Only 1 patient with a perforated appendix died, a mortality of 1 per cent for the ruptured appendices and 0.12 per cent for the entire group of 815 appendectomies.

The postoperative routine included 100,000 units penicillin every 2 hours; Wangenstein suction drainage; and intravenous fluids, proteins, and glucose. The authors feel that the use of penicillin has contributed measurably to the low mortality and low morbidity rates in these 2 groups of patients with peritonitis.

LEMUEL C. MCGEE.

PROGRAM OF AMERICAN GASTROENTEROLOGICAL  
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ATLANTIC CITY, N. J.

FRIDAY MORNING, JUNE 3, 1949

*Contributions on Gastric Secretion*

1. Nocturnal Gastric Secretion in Normal and Duodenal Ulcer Patients on Various Forms of Therapy.

HERBERT C. BREUHAUS, JAMES B. EYERLY, and (by invitation) OSMUND H. AKRE, Chicago.

2. The Quantitative Determination of Inhibitors of Gastric Secretion and their Occurrence in Gastric Juice and Gastric Mucin.

CHARLES F. CODE, and (by invitation) C. M. BLACKBURN, GEORGE B. LIVERMORE, and HENRY V. RATKE, Rochester, Minnesota.

3. The Estimation of the Potassium Content of the Gastric Juice.

LAY MARTIN, Baltimore.

4. Is Parietal Cell Secretion Inhibited by Acidosis?

VICTOR W. LOGAN, Rochester, N. Y.

5. Gastric Secretion and Radiation Effect Studied with Radio-active Iodine.

J. B. TRUNNELL (by invitation), New York City.

Discussion to be opened by FRANKLIN HOLLANDER, New York.

*Symposium on Radio-active Substances*

6. Studies on Adrenal Cortical Function in Cancer.

EDWARD C. REIFENSTEIN, JR., and BENEDICT J. DUFFY (by invitation) and MILTON S. GROSSMAN (by invitation), New York.

7. The Uptake of Radio-Active Phosphorus by Gastric Carcinoma in the Human.

SEYMOUR J. GRAY, JOHN SCHULMAN, and MARLENE FALKENHEIM (by invitation), Boston.

8. Studies on the Absorption of Barium from Barium Sulfate Suspensions.

LATHAN A. CRANDALL, JR., Elkhart, Ind.

9. Studies on Acute Surgical Nutritional Disorders With the Aid of Isotopes.  
FRANCIS D. MOORE (by invitation), Boston.  
Discussion to be opened by DR. LEON SCHIFF, Cincinnati.

10. Some Data on the Method of Computing the Volume of the Gall Bladder.  
GERALDO SIFFERT (De Paul e Silva) Rio de Janeiro.

11. The Bromsulphalein Excretion Test in Massive Gastrointestinal Bleeding.  
FRANKLIN W. WHITE and (by invitation) NORMAN ZAMCHECK and  
THOMAS C. CHALMERS, Boston.

12. Observations on a Patient With Pancreatic Fistula.  
(by invitation) EDWARD A. NEWMAN and MILTON EISENSTEIN, Chicago.

FRIDAY AFTERNOON

*Symposium on the Small Intestine*

13. Gastroenteritis in Man Due to a Filtrable Agent.  
IRVING GORDON, HOLLIS S. INGRAHAM, ROBERT KORN, and RAY E.  
TRUSSELL (by invitation) New York.

14. Rapid Method for Radiography of the Intestine.  
(by invitation) SIDNEY WEINTRAUB, and ROBERT J. WILLIAMS, New  
York City.

15. The Management of Regional Ileitis.  
EVERETT D. KIEFER, Boston and, (by invitation) M. PORTER BROLSMA,  
Omaha.

16. Streptomycin Therapy in Gastrointestinal Tuberculosis.  
WALTER R. JOHNSON, Asheville, North Carolina.  
Discussion to be opened by WALTER L. PALMER, Chicago.

17. The Action of Lysozyme on Gastrointestinal Mucosa.  
M. I. GROSSMAN, and (by invitation) K. J. WANG, Chicago.

18. Psychodynamics and Psychoanalysis in Chronic Ulcerative Colitis.  
GEORGE E. DANIELS, New York.

19. Ulcerative Colitis: A Study of Personality Types in Relation to the Various Types of Ulcerative Colitis.

VINCENT P. MAHONEY, MARGARET INGRAM, WARREN HUNDLEY, JOSEPH C. YASKIN (by invitation), and H. L. BOCKUS, Philadelphia.

20. The Use of Dibenamine in Anxiety States with Gastrointestinal Manifestations.

ALBERT J. SULLIVAN, New Orleans.

Discussion of papers 18, 19 and 20 to be opened by STEWART WOLF, New York, and T. GRIER MILLER, Philadelphia.

21. Comparison of the Chlyomicron Curve in Young and Old People.

G. A. BECKER (by invitation), and H. NECHELES, Chicago.

22. Motility and Pain Sensitivity of Abdominal Viscera After Lumbo-dorsal Sympathectomy.

JOHN R. BINGHAM (by invitation), Boston.

#### EXECUTIVE SESSION

SATURDAY MORNING JUNE 4, 1949

23. President's Address. ALBERT F. R. ANDRESEN

24. The Value of Choline and Methionine in the Treatment of Certain Forms of Liver Disease.

DAVID CAYER, and (by invitation) W. E. CORNATZER, Winston-Salem, N. C.

25. Serum Globulin Fractions as an Index of Hepatic Dysfunction.

M. A. SPELLBERG, and (by invitation) CLARENCE COHEN and WILLIAM Q. WOLFSON, Chicago.

26. Clinical Experience with the Colloidal Red Test.

HECTOR DUCCI, Santiago, Chile.

27. A Study of the Electrophoretic Pattern and Liver Function Tests in Patients who Recovered from Hepatitis.

HENRY A. RAFSKY, and (by invitation) CHARLES I. KRIEGER, MICHAEL WEINGARTEN, and BERNARD NEWMAN, New York.

28. Portal Pressure, Lymph Flow and Ascites as Influenced By Experimental Alteration of Hepatic Blood Circulation.

JESSE L. BOLLMAN, Rochester, Minn.

29. An Evaluation of Needle Biopsy of the Liver in the Differential Diagnosis of Jaundice.

LEON SCHIFF, Cincinnati.

30. Incidence and Nature of Hepatic Disturbances.

JOHN R. NEEFE, and (by invitation) HUGO DUNLAP SMITH, SAMUEL C. WILLIAMS, JR., Philadelphia.

Discussion of papers on the liver to be opened by E. N. COLLINS, Cleveland, JOHN G. MATEER, Detroit, A. M. SNELL, Rochester, Minn., and JEROME LEVY, Little Rock, Arkansas.

### *Tumors of the Stomach*

31. Tumors of the Stomach, Benign and Malignant other than Carcinoma.

HAROLD L. THOMPSON, and (by invitation) JOSEPH M. OYSTER, Los Angeles.

32. The Cytologic Diagnosis of Gastric Cancer.

JACOB MEYER, and (by invitation) JEROME M. SWARTS, ARTHUR BERNSTEIN, and ALEX RAGINS, Chicago.

33. The Differential Diagnosis of Benign and Malignant Lesions of the Stomach by Means of the Flexible Operating Gastroscope.

EDWARD B. BENEDICT, Boston.

34. Gastric Polyps.

JAMES B. CAREY, and (by invitation) LYLE HAY, Minneapolis.

35. The Role of Gastroscopy in the Diagnosis of Upper Gastrointestinal Hemorrhage of Obscure Origin.

A. M. OLSEN (by invitation), and H. J. MOERSCH, Rochester, Minn.

Discussion to be opened by H. M. POLLARD, Ann Arbor and B. B. CROHN, New York.

### SATURDAY AFTERNOON

36. Report of Committee on Peptic Ulcer.

DAVID J. SANDWEISS, Detroit.

37. Report of Subcommittee on Vagotomy.

SARA M. JORDAN, Boston.

38. Report of Committee on Hormones.

A. C. IVY, Chicago.

39. Report of Committee on Psychosomatic Aspects.  
T. GRIER MILLER, Philadelphia.
40. The Use of a Flexible Tube in the Diagnosis and Treatment of Disorders of the Esophagus.  
EDWIN BOROS (by invitation), New York.
41. Gastroscoy as an Adjunct to Photofluorography in the Early Diagnosis of Gastric Malignancy.  
MOSES PAULSON, and (by invitation) JOHN F. ROACH, Baltimore.
42. Late Sequelae in Gastroenterostomy Used in Treatment of Congenital Pyloric Stenosis.  
JOEL M. BAKER, Seattle, Washington.  
Discussion to be opened by WALTMAN WALTERS, Rochester, Minn., and SAMUEL F. MARSHALL, Boston.

*Symposium on Some Aspects of Peptic Ulcer*

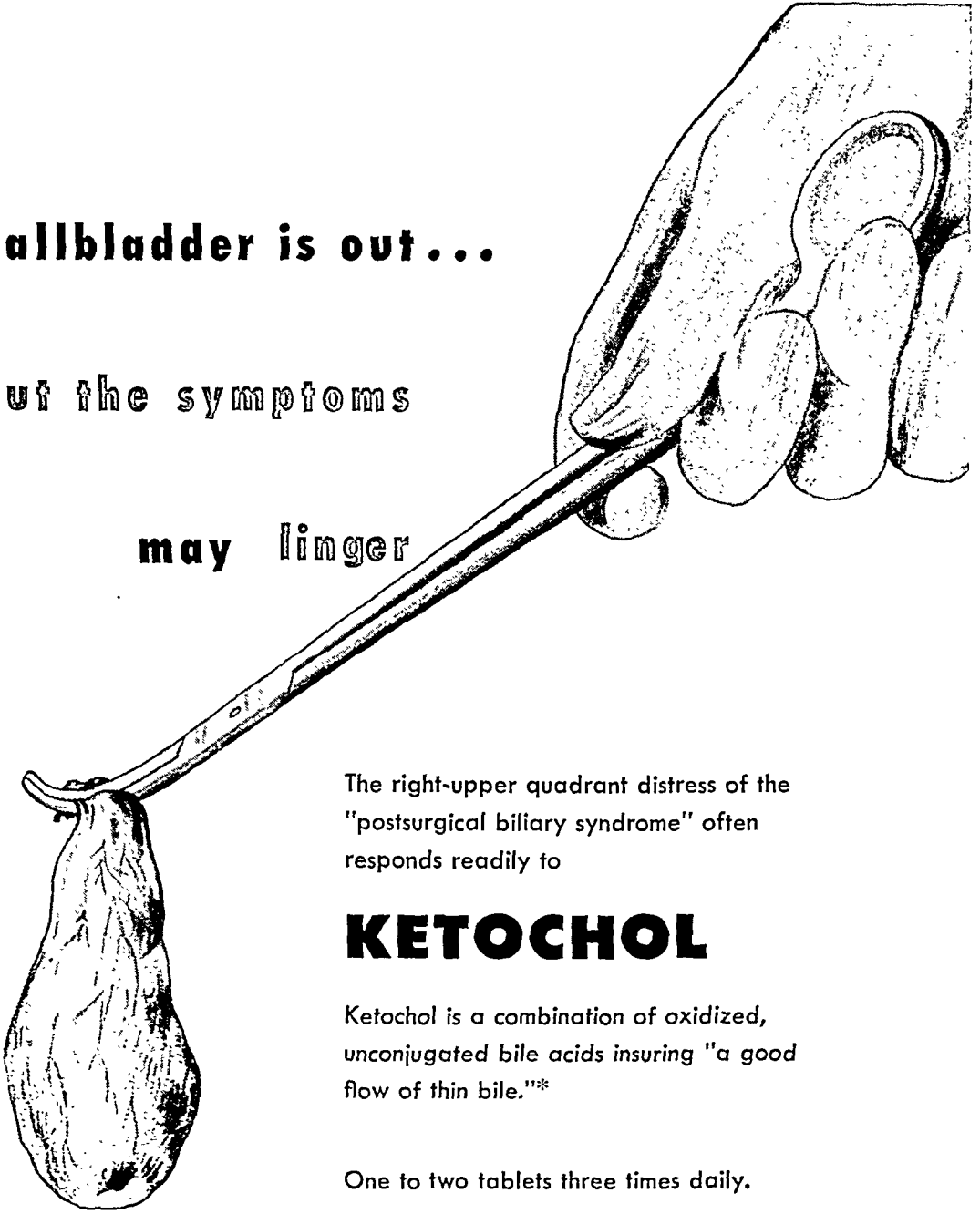
43. Perforation Complicating Duodenal Ulcer: A Consideration of Some Unusual Forms of Perforation.  
MAURICE FELDMAN, Baltimore.
44. The Effectiveness of Orally Administered Enterogastrone in the Relief of Symptoms Due to Duodenal Ulcer.  
EARL E. GAMBILL, CARL G. MORLOCK, HUGH R. BUTT, CHARLES F. CODE, and (by invitation) ERIC E. WOLLAEGER, Rochester, Minn.
45. Correlation of Insulin Test Studies and Clinical Results in a Series of Peptic Ulcer Cases Treated by Vagotomy.  
VERNON WEINSTEIN (by invitation), and FRANKLIN HOLLANDER and RALPH COLP, New York.
46. Experimental Production of Peptic Ulcer and Dietary Deficiency and Treatment of Ulcer as a Deficiency Disease.  
GARNETT CHENEY (by invitation), San Francisco.  
Discussion to be opened by GEORGE B. EUSTERMAN, Rochester, Minn., DAVID J. SANDWEISS, Detroit, A. C. IVY, Chicago, and JULIAN M. RUFFIN, Durham, N. C.
47. Mechanism of the Post-Gastrectomy Dumping Syndrome.  
THOMAS E. MACHELLA, Philadelphia.  
Discussion to be opened by MANDRED W. COMFORT, Rochester, Minn.



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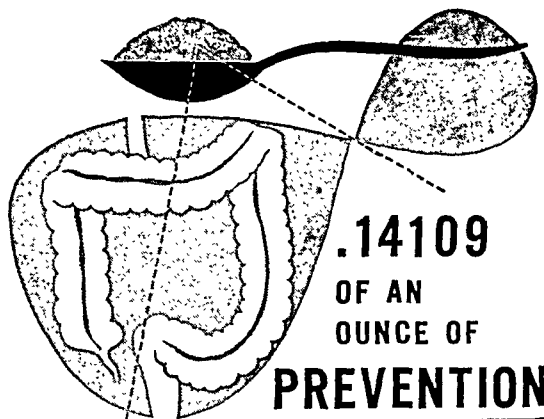
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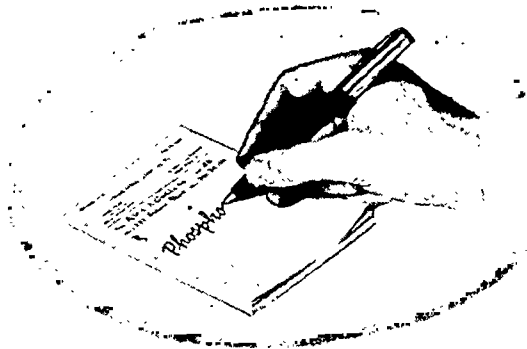
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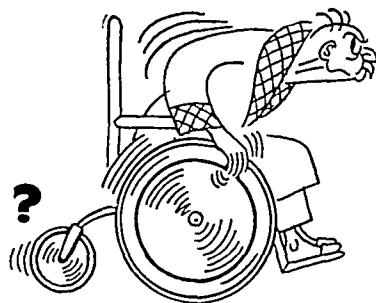
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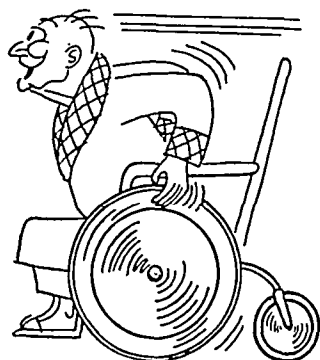
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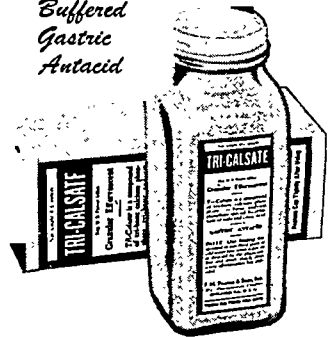
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## *Information Regarding Post-Graduate Instruction in Gastroenterology*

At the request of the Board of Governors of the American Gastroenterological Association, Dr. Julian M. Ruffin wrote the members of the Association to ascertain those members and institutions which were able to provide a short course or extended graduate study in Gastroenterology. The following have responded.

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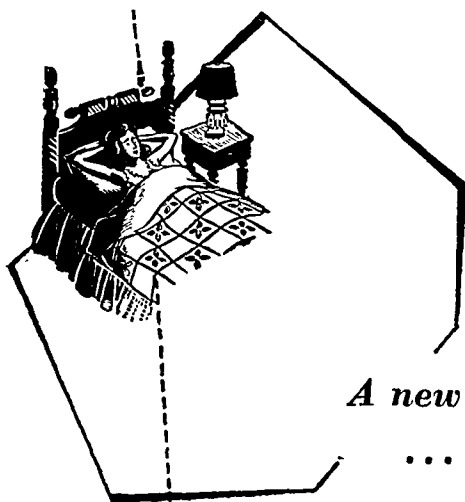
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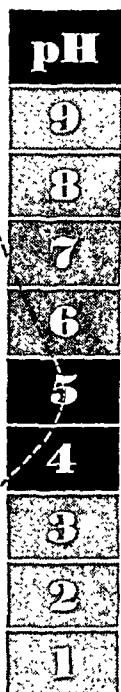
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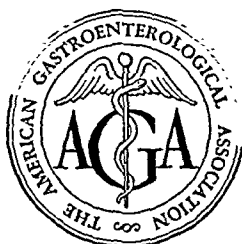
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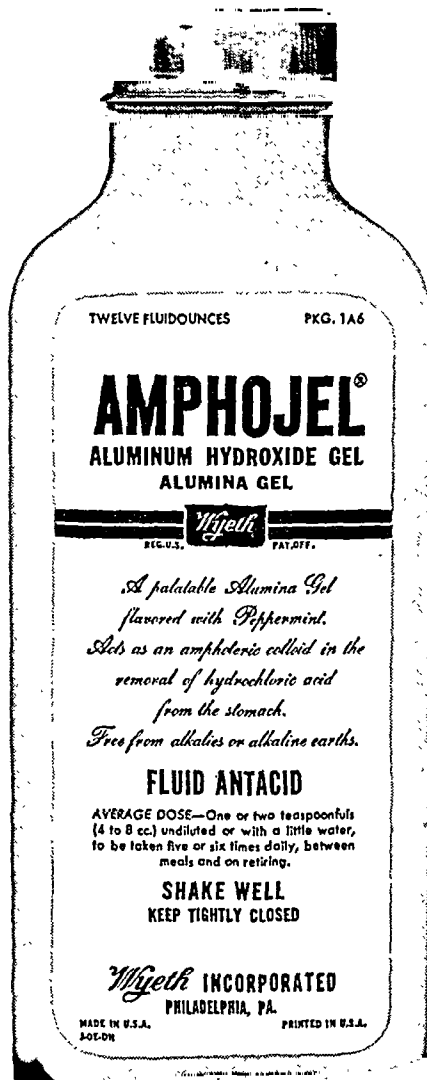
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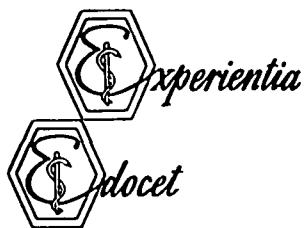
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\*Holbert, J. M., Noble, N. and Grote, I. W.: *A Study of Antacid Buffers. II. Prolonged Neutralization*, J. Am. Pharm. A. (Sci. Ed.) 37:292, 1948.



Data in graph from Krantz et al.: J. Pharm. & Exper. Therap. 82:247, 1944. 0.5 Gm. dihydroxy aluminum aminoacetate in 25 cc. synth. gastric juice.

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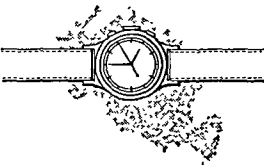
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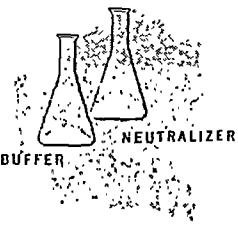
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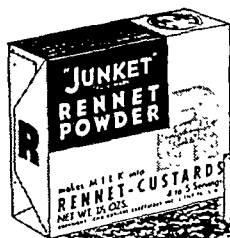
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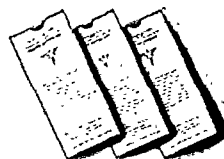


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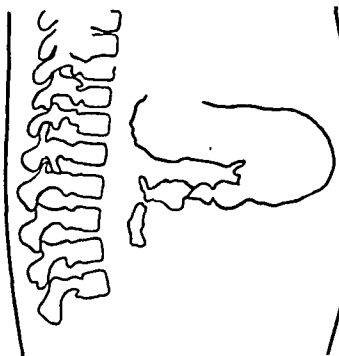
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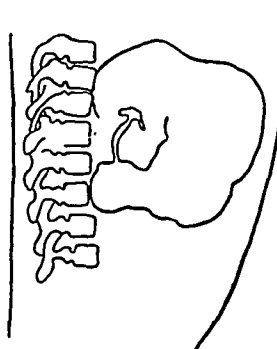


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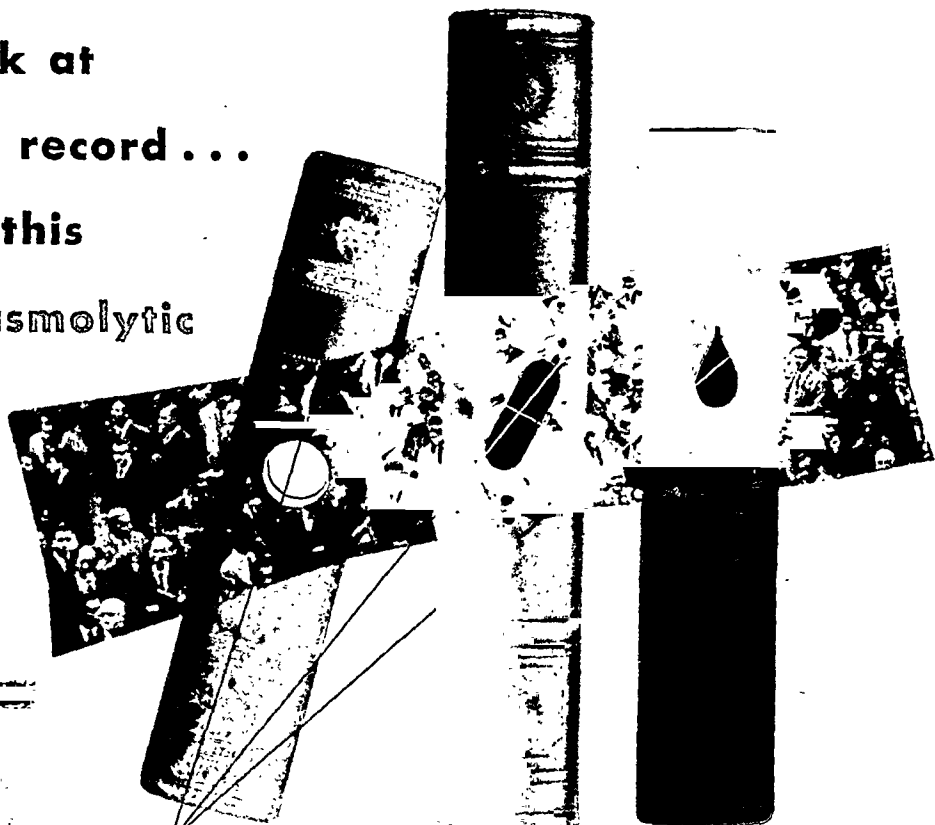
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1. Kilstein, R. I.:  
Rev. Gastroenterol.,  
14:171, 1947.
2. Morrissey, J. H.:  
J. Urol.,  
57:635, 1947.
3. Ricci, J. V.:  
In The City Hospital Year Book,  
1946, New York, 1947.

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<sup>1</sup>Cannon, P. R.; Steffee, C. H.; Frazier, L. J.; Rowley, D. A., and Stepto, R. C.: The Influence of Time of Ingestion of Essential Amino Acids upon Utilization in Tissue Synthesis, *Fed. Proc.* 6:390, 1947.

<sup>2</sup>Geiger, E.: The Role of the Time Factor in Feeding Supplementary Proteins, *J. Nutrition* 36:813 (Dec. 10) 1948.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



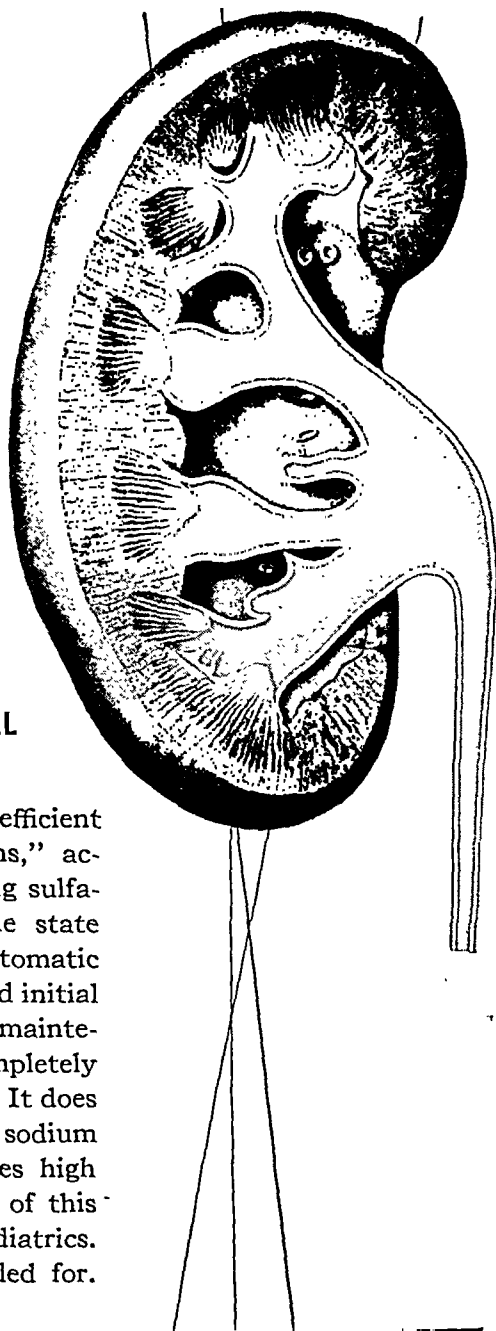
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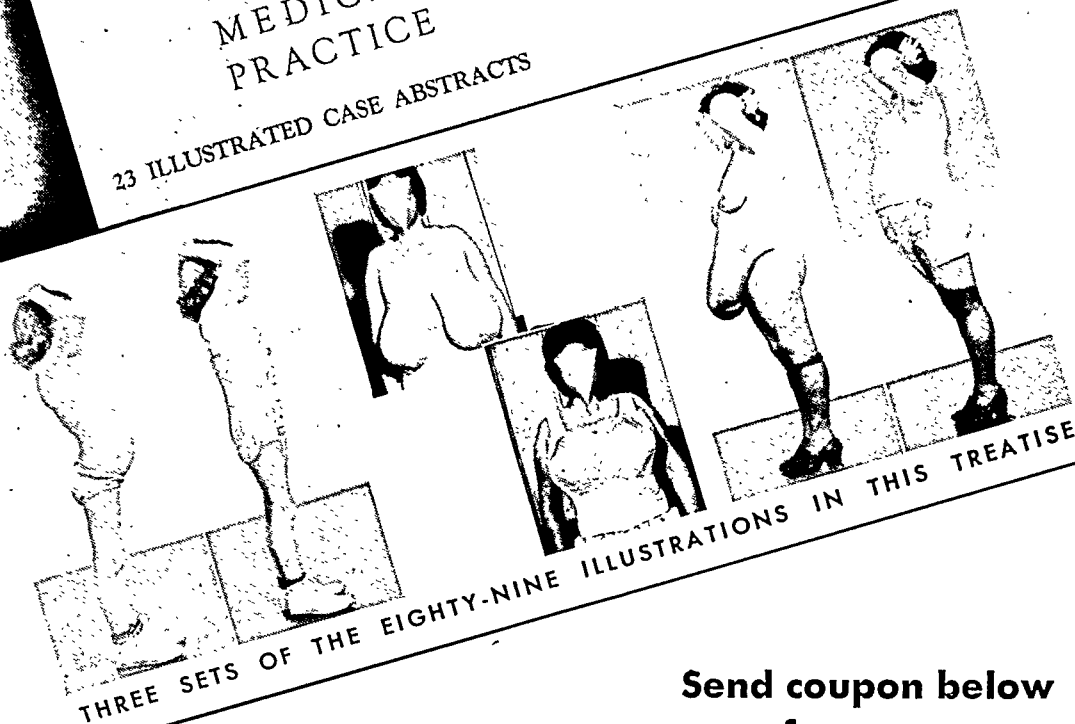
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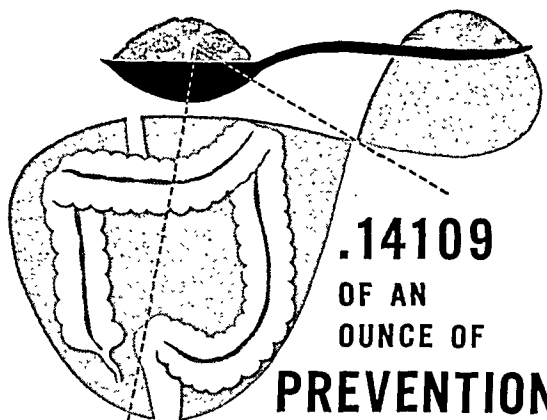
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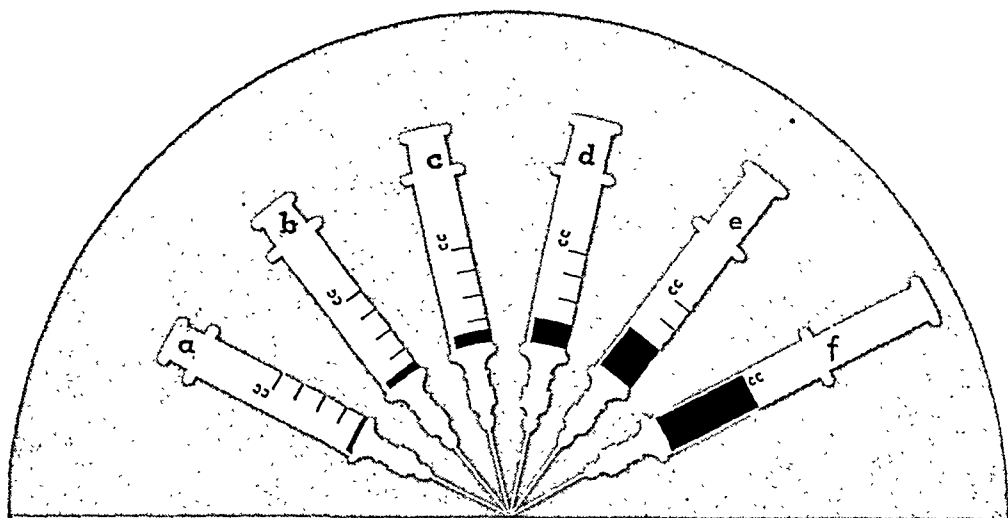
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# GASTROENTEROLOGY

*Official Journal of the American Gastroenterological Association*

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VOLUME 12

April 1949

NUMBER 4

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## RECENT ADVANCES IN GASTROINTESTINAL PHYSIOLOGY\*

J. E. THOMAS, M.D.

*From the Department of Physiology, Jefferson Medical College of Philadelphia*

### INTRODUCTION

The recent advances in gastrointestinal physiology selected for this discussion have been in three principal fields of study: First, the increase in our knowledge of the importance of the nervous system as a regulator of gastrointestinal function; this development has been associated with widespread speculation regarding the possible nervous origin of some gastrointestinal diseases. Second, the more recent developments in the study of gastrointestinal hormones; these, likewise have been exploited clinically. Third, the evidence that is beginning to appear of the interdependence of neural and humoral mechanisms.

### I. ADVANCES IN NEUROPHYSIOLOGY

*Peripheral autonomic nerves.* The concept of the autonomic innervation of the gastrointestinal organs proposed by Gaskell<sup>1</sup> has long been known to be inadequate, particularly his idea of a consistent antagonism between the sympathetic and parasympathetic innervation<sup>2</sup>. The evolution of a more rational viewpoint has been advanced through a recent review by Professor Bakbin<sup>3</sup>, in which he calls attention to the difficulty of demonstrating antagonistic innervation of the digestive glands. He concludes that "It is much easier to observe the synergism of the sympathetic and parasympathetic impulses to the glandular tissue than their mutual antagonism." Since this statement could also be applied to much of the gastrointestinal muscle<sup>4</sup>, we may perhaps at last abandon the naive notion that the function of the autonomic fibers is determined by their anatomic origin and course. There is enough evidence to warrant the conclusion that the autonomic nervous system is a functional unit in which individual sympathetic and parasympathetic fibers are used to increase or decrease function without regard to their anatomic origin but in accord with the needs of the organism<sup>5, 6</sup>.

The greatest activity recently in the study of gastrointestinal innervation

\* Read before the Section on Pathology and Physiology at the Ninety-Seventh Annual Session of the American Medical Association, June 24, 1948.

has centered around the functions of the abdominal vagus, particularly in human subjects. Interest was aroused in this problem by the proposal of Dragstedt and Owens<sup>7</sup> to section the vagus nerves in patients with peptic ulcer. The history of this procedure and some of its physiological aspects have been the subjects of recent reviews<sup>8, 9</sup>. We are not here concerned with the therapeutic results of this operation, though it may be remarked that the clinical reports so far received are optimistic; but as an experiment in human physiology on an unprecedented scale it demands our most careful consideration.

In the human, the nerves have been cut either directly above (transthoracic) or below (transabdominal) the diaphragm. Hence the vagus fibers that end in the esophageal portion of the myenteric plexus<sup>10</sup> or those that may become buried in the wall of the esophagus<sup>11</sup> are not severed. This is an important consideration because in animal experiments the depression of gastric functions that follows vagotomy is much more severe when the nerves are cut above the hilus of the lung<sup>12</sup> than when they are cut near the level of the diaphragm<sup>13, 14, 15</sup>. Pavlov and his co-workers<sup>12</sup> found that after the nerves had been severed above the root of the lung in dogs gastric digestion was inadequate to sustain life on an ordinary diet. This difficulty is rarely encountered in animals after transthoracic vagotomy. It appears that the vagus innervation that remains after transthoracic vagotomy, although it may be inadequate to mediate a measurable response to specific stimuli such as insulin hypoglycemia<sup>16</sup> is, nevertheless, of vital importance since it sustains in some way the minimal secretory and motor activity of the stomach that is essential for survival without special care.

The most obvious physiological change in patients following vagotomy is profound depression of gastric motility and secretion<sup>17, 18, 19, 20, 21, 22, 23</sup>. Although the motor changes tend to disappear within a year gastric retention has persisted in some patients for from 11 months<sup>21</sup> to 2½ years after operation; total absence or abnormality of peristalsis has been especially noticeable<sup>23</sup>. In the series of patients reported by Grimson and others<sup>23</sup>, all of whom had free HCl in their gastric juice before operation, 4 were still achlorhydric 2½ years after operation. Moore and his co-workers<sup>23</sup> found that the decrease in total and free acid was persistent in most of their patients.

These changes, though less severe than those that follow high vagotomy in dogs, are considerably more persistent than the effects seen in animals when the operations are done at a corresponding level<sup>13, 14, 15</sup>. This may mean that it is possible to accomplish a more nearly complete vagotomy in the human but it seems more probable that in man the gastrointestinal organs have lost some of their autonomy and are more dependent on their extrinsic innervation.

A certain percentage of vagotomized patients develop a more or less severe

diarrhea which, although usually temporary, may be persistent<sup>23</sup>. Many report relief of constipation and nearly all a change in bowel habit with a tendency toward softer, more frequent stools. This is a surprising result in view of the prevalent belief that the vagus conveys chiefly motor fibers to the stomach and small intestine. The effects on the bowel may merely indicate the inadequacy of gastric digestion and result from passage into the intestine of unsterilized, undigested, fermenting or putrid gastric contents but there is reason to believe that they may have a deeper significance. Pavlov<sup>24</sup> considered that extreme vulnerability of the intestine was one of the consequences of vagotomy most dangerous to life. It is noteworthy also that Alvarez and his co-workers<sup>8, 25</sup> found an overly active bowel with abnormally frequent peristaltic rushes in chronically vagotomized rabbits. He concluded that, "Much of the evidence available indicates that both the vagi and splanchnics serve as brakes to keep the bowel from being too irritable and responsive to every stimulus"<sup>8</sup>.

The functioning of the pancreas after vagotomy has, apparently, not been investigated in the human. In vagotomized dogs Crider and Thomas<sup>26</sup> found a significant decrease in the output of nitrogenous substances (enzymes) from the pancreas due chiefly to a decrease in the volume of the juice, when acid or peptone was used as a stimulus. The response to soap remained normal both in volume and enzyme output. In a preliminary study on one dog, Pincus and others<sup>27</sup> found that the output of enzymes (measured as total nitrogen) was reduced by 60 to 80 per cent following transthoracic vagotomy. Their experiments were so designed that the delayed gastric emptying as well as the vagal denervation of the pancreas influenced the results.

Snape<sup>28</sup> has reported that emptying of the gall bladder in dogs after instillation of cream, fatty acids, casein, skimmed milk or peptone into the duodenum was delayed but not seriously impaired after vagotomy. The effects of vagotomy on the biliary tract, on liver function in general, on intestinal secretion and absorption, on the insulin mechanism, and especially the long term effects on all gastrointestinal functions remain to be studied.

*Central autonomic mechanisms.* One of the outstanding developments in recent years in the field of gastroenterology has been the growing tendency to associate gastrointestinal diseases with specific emotional patterns in the patient. The influence of pleasant<sup>29</sup> or unpleasant<sup>30</sup> emotional experiences on the functioning of the digestive organs is well known and the part played by the latter in the etiology of functional gastrointestinal disturbances is generally recognized<sup>31, 32</sup>. The current development envisages the possibility that emotional stress, if severe enough or when acting in susceptible individuals, may lead to organic disease, notably peptic ulcer<sup>31, 33, 34, 35, 36, 37, 38</sup> or ulcerative colitis<sup>33, 39, 40, 41, 42, 43</sup>.

The interest of the physiologist in this problem is in the neural mechanisms that underlie both the emotional patterns and the visceral changes thought to be associated with them. He would contend that subjective feelings, no matter how intense, cannot of themselves elicit visceral responses. Excluding for the moment the role of hormones, such responses are brought about by nerve impulses impinging on effector organs such as muscle or gland cells. These impulses must arise as a result of specific stimuli, either present in the environment or recalled from past experience. In either case they are limited in their travel to existing chains of neurones and the effects they produce must be within the physiologic potential of the effector organs. While it is true that the excitatory process, apparently while traversing certain central mechanisms, may give rise to subjective phenomena which we call feelings or emotions these manifestations are to be regarded as an additional effect and not the cause of the excitation. As Papez<sup>44</sup> has pointed out, the term *emotion* implies both a "way of acting" and a "way of feeling." The "way of acting" involves both visceral and somatic expression. It is the visceral component of the "way of acting" that does the damage and not, we believe, the "way of feeling."

We should like, therefore, in the study of neurogenic disease to identify, first the stimulus, second the neuronal path over which the resultant impulses travel and finally to analyze the response of the effector organ. This, in substance, is the study of reflexes, conditioned or inborn, and we believe that such study provides the most rational approach to the problems of psychosomatic medicine.

The idea that emotional expression may be a conditioned response has recently been emphasized by Babkin<sup>45</sup>. This principle may be illustrated by the familiar example of the soldier who has been subjected to repeated bombing attacks. During the actual bombings fear is an instinctive response because the danger from concussion and flying missiles is real; but associated with the real danger is another stimulus, not in itself a menace but always present along with the real danger—the drone of airplane motors overhead. Eventually, in some individuals, this sound alone comes to be a conditioning stimulus capable by itself of eliciting all the manifestations of terror that occurred during the actual bombings. It is easy to imagine similar, even though less spectacular, relations in our more common experiences. As Babkin<sup>45</sup> pointed out, if the conditioning stimulus is frequently or constantly present it may keep "hammering away" at the receptive mechanism until the emotional response becomes chronic.

Considerable progress has been made in recent years in the study of the central neural mechanisms involved in the visceral and somatic manifestations of emotion. The early experiments by Bard<sup>46</sup> in which the syndrome called sham rage was demonstrated in animals after excision of the entire brain cranial

to the hypothalamus served to emphasize the importance of this latter area as a center for emotional expression. The manifestations which he observed included all the visceral and somatic responses characteristic of an animal in a violent rage although the parts of the brain commonly assumed to be involved in subjective experience were removed. When the hypothalamus itself was separated from the brainstem the manifestations ceased. He interpreted the visceral reactions as being due to activation of the sympathetic division of the autonomic system<sup>47</sup>. The following year Fulton and Ingraham<sup>48</sup> showed that a chronic state in which visceral and somatic manifestations of fury can be elicited by mild stimuli develops in cats after a limited operation designed to sever the connections between the frontal lobes of the cerebrum and the hypothalamus.

Studies by Ranson and his associates<sup>49</sup>, by the method of localized stimulation, showed that visceral changes characteristic of the activity of the sympathetic autonomies could be elicited from various points in the hypothalamus. Later studies<sup>50</sup> suggested the presence of vagal centers for the gut at or behind the infundibular level but centers for mass discharge over the parasympathetics comparable to those for the sympathetics have not, apparently, been demonstrated.

Hess and others (cited by Ingram<sup>51</sup>) have stimulated various parts of the hypothalamus in unanesthetized animals by means of implanted electrodes. They were able to elicit complicated performances involving coordination of somatic and visceral functions such as defecation and urination. These authors oppose the concept of topographically circumscribed centers in the hypothalamus and prefer to regard it as a coordinating mechanism for activities involving simultaneous visceral and somatic expression.

From all these observations it is possible to conclude that the hypothalamus dominates the autonomic outflow from the central nervous system and is much more intimately related to the psychic and somatic functions than are the medullary and spinal autonomic centers.

In this relation the connections of the hypothalamus with the cortex and other cerebral gray matter is of the greatest interest. The numerous fiber tracts to and from the hypothalamus have been described in detail by Kuntz<sup>10, 52</sup> who also cites the extensive literature. The potential connections with the neocortex are of particular interest from the standpoint of psychosomatic medicine. These have recently been studied in detail by Murphy and Gellhorn<sup>53</sup> who studied the distribution of action potentials resulting from the local application of strychnine to various points in the cortex, the thalamus and hypothalamus.

In discussing their results they state that certain of the conducting paths which they demonstrated may be said to be tracts of "preferential discharge",

by which they mean low resistance pathways. These were paths from the hypothalamus, anterior or posterior to the dorsomedial thalamus and from the dorsomedial thalamus to the cortex; from the ventrolateral thalamus to the hypothalamus; from the cortex (prefrontal, motor, sensory, cingulate) to the dorsomedial thalamus and the hypothalamus, anterior or posterior. The authors suggest that these two-way conduction paths between cortex and hypothalamus may constitute, under some circumstances, "reverberating circuits" and it seems possible that if this is true, and if a given circuit may have its resistance further lowered by conditioning, the response to the conditioning stimulus may be so augmented, particularly with regard to its emotional content, as to be wholly out of proportion to the strength of the stimulus.

Assuming that appropriate stimuli and conducting paths are available, we may ask whether the resultant impulses induced in the neurons of the autonomic system are capable of causing organic disease. We can give an answer free from conjecture only with respect to peptic ulceration of the gastric and duodenal mucosa. The now familiar observations of Cushing<sup>54</sup> and the subsequent experiments reported by Keller<sup>55</sup> leave little doubt that disturbances in the autonomic innervation induced by operative trauma at the hypothalamic level can lead to hemorrhagic and ulcerative lesions of the stomach and duodenum. Keller's experiments were done on dogs in which he was making hypothalamic lesions in the course of a study of the temperature regulating centers. Like Cushing's patients with comparable lesions, many of these animals developed ulcers or hemorrhagic spots in the gastric or intestinal mucosa. Keller also studied the protective effect of vagotomy or sympathectomy. Vagotomy gave complete protection from the ulcerative lesions but not from the occurrence of hemorrhagic spots. Ulcers but no hemorrhagic spots were seen after sympathectomy.

The favorable results of vagotomy in chronic peptic ulcer as it occurs in man, provide corroborative evidence. Although these human experiments do not prove that vagus nerve impulses are involved in the etiology of the ulcers they certainly leave little room for doubt that such impulses contribute to the chronicity of the disease.

## II. HORMONES

Among the numerous physiologically active substances derived from the gastric or intestinal mucosa secretin, pancreozymin and gastrin have received recent attention. Enterogastrone is also being investigated from the standpoint of its possible usefulness in ulcer disease as are various non-specific intestinal extracts.

*Secretin and pancreozymin.* The use of purified secretin intravenously as a test of pancreatic function has had extensive clinical trial<sup>56,57</sup> and has proved to

be a valuable diagnostic aid, particularly in advanced pancreatic disease<sup>57</sup>. The development of a relatively simple method for its preparation<sup>58</sup> and of a domestic manufacturing source promises to make this interesting material more readily available to American physicians in the near future.

Pancreozymin is the name given by Harper and Raper<sup>59a</sup> to a product which they obtained from crude preparations of secretin (intestinal extracts). It increases the output of enzymes from the pancreas when given intravenously but is devoid of secretin action, that is, it does not increase secretion of fluid and bicarbonate. The observations of Harper and Raper were promptly confirmed by Greengard, Ivy and their co-workers<sup>60</sup>. Recently Harper and MacKay<sup>59b</sup> have compared the effects of pancreozymin with the effects of vagal stimulation on the pancreas and found them very similar in that both increase the output of enzymes from the pancreas and both cause depletion of the zymogen granules of the acinous cells. They differ in that the effects of pancreozymin are not abolished by atropine which, of course, prevents the effects of vagal stimulation. Whether or not pancreozymin takes part in the normal regulation of pancreatic function remains to be determined.

*Gastrin.* The existence of a gastric secretory hormone other than histamine was indicated by the work of Komarov<sup>61</sup> in 1938. His findings have since been confirmed independently in several laboratories<sup>62,63,64,65</sup>. Gastrin is present in largest amount in the mucosa of the pyloric portion of the stomach but small yields are also obtained from the duodenum<sup>61,63</sup>. None has been found in the body of the stomach or lower intestine. Methods of extraction used by different investigators have varied but it is interesting that all are methods which, when applied to the duodenal mucosa, yield secretin. The active material is therefore probably similar to, but certainly not identical with, secretin. Proof that the active principle is not histamine is provided by the facts that, unlike histamine, gastrin is not diffusable through cellophane<sup>63</sup>, does not lower blood pressure<sup>63,64</sup>, and is destroyed by peptic digestion<sup>63</sup>. Active preparations have given negative results when subjected to the usual biological tests for histamine<sup>61</sup>.

*Enterogastrone and urogastrone.* The name *enterogastrone* was first used to characterize the humoral agent that inhibits gastric secretion when fat is present in the intestine<sup>66</sup>. Since fat also inhibits gastric motility it was generally believed, but without proof, that this action was also due to enterogastrone. Later it was found that one or more substances present in urine also inhibit gastric secretion and motility<sup>67,68,69,70</sup> and the term *urogastrone*<sup>71</sup> was used to characterize this activity. Subsequent work (for literature see Sandweiss<sup>72</sup>) has shown that enterogastrone and urogastrone are not identical substances although they may be related and that the secretory depressant and the agent that inhibits motility are probably different substances.



Current interest in these agents arises from the fact that various intestinal and urinary extracts may possibly be of value in the treatment of ulcerative disease of the gastrointestinal tract. Extensive reviews by Sandweiss<sup>72</sup> in 1945 and by Greengard, Atkinson, Grossman and Ivy<sup>73</sup> in 1946 described the results of experimental therapy of peptic ulcer with urinary extracts<sup>72</sup> and enterogastrone<sup>73</sup> previous to those dates. The experimental work cited in these reviews leaves no doubt that both intestinal and urinary extracts are capable of preventing or curing the type of experimental jejunal ulcer that develops in dogs following the Mann-Williamson operation of diverting the bile, pancreatic juice and duodenal secretions into the lower ileum. The nature of the curative agent is obscure but it is probably not the substance or substances originally identified as enterogastrone and urogastrone since the therapeutic effects of the extracts appear not to depend on their action as gastric secretory depressants. For this reason Sandweiss<sup>72</sup> has suggested calling the anti-ulcer factor in urine *anthelone* while reserving the term *urogastrone* for the gastric secretory depressant. A similar clarification of the terminology applied to intestinal extracts would be useful.

Results obtained to date in patients, although encouraging, are far less positive than the results obtained in experimental animals. Sandweiss<sup>72</sup> concludes that "To date these ulcer protective factors are not sufficiently concentrated or purified to warrant extensive clinical use." Greengard, Ivy and their co-workers<sup>73</sup> are somewhat more optimistic but still cautious. They report that, "Therapeutic trial—on 58 patients—has demonstrated the probability that the material (enterogastrone) is effective in preventing recurrences during the period of its administration, and for a length of time thereafter of a duration as yet undetermined." Active work with intestinal and urinary extracts is in progress in several laboratories but from the paucity of recent reports one may conclude that no one has yet found among the hormones a positive cure for peptic ulcer in humans.

Several recent studies on animals have been concerned with the ulcers that develop in the rumen of rats when the pylorus is ligated. The practice of ligating the pylorus for the collection of gastric juice in rats was introduced by Roe and Dyer<sup>74</sup> and adapted by Friedman<sup>75</sup> and Friedman and Sandweiss<sup>76</sup> to the study of gastric secretory stimulants and depressants. Shay, Komarov and others<sup>77</sup> observed that rats prepared in this way developed ulcers of the rumen within a period of 18 hours or less; these authors proposed the use of the method for the assay of hormonal anti-acid and anti-ulcer agents. Morris, Grossman and Ivy<sup>78</sup> have recently reported that "enterogastrone" fails to protect rats prepared in this way from the development of ulcers of the rumen. On the other hand Wick and co-workers<sup>79</sup> have described a method of preparing a urine extract which is fully protective in the rat. Risley and others<sup>80</sup> re-

port that both "enterogastrone" and various urinary extracts afford appreciable protection from ulceration of the rumen in these animals. It is interesting to note that they found the anti-ulcer activity of the preparations they used to closely parallel the depression of acid secretion. Since this is contrary to the previous findings in experimental ulcer in dogs it may indicate that the rat ulcers are not comparable to Mann-Williamson ulcers in dogs.

The experimental work to date leaves little room for doubt that the intestinal mucosa contains material of some sort capable of causing increased resistance to ulceration. The active agent may be a hormone, an essential nutrient, a growth stimulant, an enzyme inhibitor or a protective agent of a character as yet unimagined. It is probable that progress in its isolation and utilization may be more rapid once we abandon our efforts to identify it with a known hormone.

In this connection the experience of several Swiss investigators is of interest. They have been treating ulcers with lipid and protein free extracts of whole stomach or intestine, using gastric extract for gastric ulcers and intestinal extract for duodenal ulcers. Their reported results, recently reviewed by Hubacher<sup>81</sup>, are comparable to the more optimistic results reported in this country with "enterogastrone." For example of 209 cases so far reported, 98% are said to have "reacted favorably." Of Hubacher's own patients, 44 of the 54 treated were benefited and the rate of recurrence was lower than the average. He saw 2 recurrences in 16 months, presumably among the 44 patients that were improved.

Further evidence that the intestinal mucosa yields an anti-ulceration factor which is probably not enterogastrone is provided by recently reported success in the treatment of ulcerative colitis with intestinal extracts. Apparently the first experiments along this line were done in England by Gill<sup>82</sup> whose report has recently been reviewed by Lust<sup>83</sup>. Without knowing of Gill's work similar studies were started in the Jefferson proctologic clinic by Friedman, Haskell and Waldron<sup>84</sup>. To date 71 cases have been treated by the Philadelphia group of which 27 have been followed for more than one year. Of these, 24 of the 26 who persisted in the treatment continue to show improvement. It is, of course well known that patients with ulcerative colitis frequently show improvement on any treatment or with no treatment at all. However, Dr. Haskell, the proctologist in this group, feels that the sustained benefit to many of these patients has not been paralleled by other forms of treatment previously at his disposal.

### III. THE INTERDEPENDENCE OF NERVOUS AND HUMORAL MECHANISM

We have been discussing nervous and humoral regulators of visceral function as though they were independent mechanisms; accumulating evidence indicates

that they are in fact closely related. One may be dependent on the other for one or more of the following reasons: (1) A particular hormone may be released only through the action of a nervous mechanism; (2) a humoral agent may act only on some part of the nervous mechanism; (3) a synergistic relationship may exist between nerves and hormones such that they exert their full effect only when acting together.

The first type of interrelationship is admirably illustrated by the familiar neurohormones, acetylcholine and sympathin, which are released through the action of the cholinergic and adrenergic nerves respectively.

There is some evidence that the hormone gastrin, likewise, may be released only in the presence of an intact vagus innervation. Zeljony and Savich<sup>85</sup> found in 1911 that the secretagogue effect of fatty acids and meat extract applied to the pyloric mucosa was prevented by atropine or by cocaineization of the mucosa. They interpreted their results as disproving the humoral theory of gastric secretion but in 1941 Gregory and Ivy<sup>86</sup> showed that cocaineizing the mucosa of the stomach prevented the liberation of the gastric secretory hormone. In their experiments an isolated, denervated pouch of the stomach normally secreted in response to chemical or mechanical stimulation of the main stomach, thus proving the existence of a gastric secretory hormone. No such effect was obtained after cocaineization or the application of procaine to the the mucosa of the main stomach. Control experiments proved that the drugs did not paralyze the secretory mechanism, hence they must have prevented liberation of the hormone.

Release of the hormone could have been prevented in the experiments just described either by paralysis of an essential nervous mechanism or through direct depression of the cells that produce the hormone, but other evidence inclines one to the view that these neurotropic drugs were exerting their usual action. If this interpretation is correct one would expect to find the chemical phase of gastric secretion depressed by vagotomy. This appears, indeed to be the case; it is difficult otherwise to explain the profound depression of secretion, often with achlorhydria, that occurs in many human subjects following section of the vagus nerves.

Hormones which seem to act on or in conjunction with peripheral nervous structures have long been known. The agent, probably a hormone, that is responsible for the secretory effect on the pancreas of soap in the intestine will serve as an example. Cutting the extrinsic nerves in no way diminishes the effectiveness of soap as a pancreatic stimulus<sup>26</sup> but its action is almost completely suppressed by atropine<sup>87</sup>. Moreover, soap solutions may be used to extract a potent pancreatic secretagogue from the intestinal mucosa, which differs from secretin in that its action is almost completely prevented by atropine<sup>88,89</sup>. Another example is the effect of an increase in blood sugar on the

secretion of enzymes by the pancreas. Experiments by Hebb<sup>80</sup> in Babkin's laboratory have shown that an increase in the glucose content of the blood increases the output of pancreatic enzymes in the rabbit and that this effect is prevented by atropine. She concludes that the glucose owes its effect to an action on the parasympathetic endings. In collaboration with Dr. Crider<sup>81</sup> we have found that various carbohydrates in the intestine increase the enzyme output from the pancreas. This effect is accompanied by an increase in the blood sugar but we have not established a causal relation between the blood sugar rise and the increase in enzyme output. In any case the effect is abolished by atropine as in Hebb's experiments.

Some degree of synergism between nervous and humoral mechanisms is to be expected when they both have the same action but the effects of combined nervous and humoral stimulation often go far beyond simple addition of effects. The action of secretin on the pancreas is increased several fold by concomitant stimulation of the vagus nerves<sup>82</sup>. We <sup>83</sup> have noted that the secretory effect on the pancreas of stimulation of the vagus nerves often disappears after ligation of the pylorus, apparently because the vagus is thus deprived of the synergistic action of the intestinal hormones normally liberated by the HCl entering the intestine from the stomach. If an effective dose of secretin is given in these circumstances the secretory action of the vagus may be restored and persist for some time after the direct action of the secretin has ceased to be apparent.

Uvnäs<sup>84</sup>, in an extensive study of the nervous and humoral mechanisms involved in gastric secretion, came to the conclusion that the nervous phase of secretion was entirely dependent on liberation of the hormone, gastrin, from the pyloric mucosa. In animals with the pylorus removed or deprived of its blood supply he was unable to elicit secretion on stimulation of the vagus nerves. Furthermore, in the intact stomach, although stimulation of the vagus alone or the administration of a gastrin preparation alone caused only a little secretion, the action of the two together caused an abundant flow of juice. Uvnäs probably went too far in drawing conclusions from experiments on anesthetized animals for Babkin and his co-workers<sup>85</sup> have been able to show that his failure to obtain a good response to vagus stimulation in his operated animals was in part due to the recent trauma of the operation. However, this criticism is applicable only to Uvnäs' negative results. Those experiments in which he obtained secretion by the combined action of gastrin and the vagus would appear to demonstrate a synergistic action, the more so because it was still evident under unfavorable conditions.

The effect of vagotomy on the response of the gastric glands to histamine may also have some significance in this connection although the part, if any, played by histamine in the normal regulation of gastric secretion is at present obscure. In the dogs studied by Vauzant<sup>86</sup> there was a decrease of from 20 to

80 per cent in the volume of gastric juice secreted in response to histamine following vagotomy. Oberhelman and Dragstedt<sup>96</sup> have recently reported similar results on dogs and in a series of patients. Many of the vagotomized patients studied by Grimson and others<sup>23</sup> likewise had a diminished secretory response to histamine. The exact interpretation of the partial dependence on the vagus innervation of the secretory effect of histamine is not clear but it is interesting in view of the close resemblance of histamine to the hormone gastrin in its action on the gastric glands.

#### SUMMARY

A survey of the recent literature dealing with gastrointestinal physiology reveals the following trends and developments:

1. The old idea of antagonistic action of the sympathetic and parasympathetic autonomies is giving way to a more rational concept involving coordination and frequent synergistic action.

2. Extensive experience with vagotomy has revealed that the depression of gastric motor and secretory functions is more persistent in the human than in experimental animals after comparable operations. The evidence suggests that complete vagotomy, if it were possible, might be dangerous.

3. The concept of the neurogenic etiology of disease is, momentarily, popular. It is suggested that a rational basis for this concept demands a demonstration of appropriate neuronal mechanisms. Recent further proof of the domination of the autonomic system by the hypothalamus and of the intimate functional relation of the hypothalamus to the neocortex contributes to the required demonstration.

4. The use of hormones or other physiologically active substances from the intestine in the diagnosis or treatment of gastrointestinal disease is still in the experimental stage.

5. Secretin promises to be useful in the diagnosis of advanced pancreatic disease.

6. The presence of an anti-ulcer factor in the intestinal mucosa has been demonstrated but its therapeutic application is proving difficult.

7. The occurrence in the pyloric portion of the gastric mucosa of a gastric secretory hormone (gastrin) other than histamine has been confirmed.

8. Recent work suggests, but does not prove, that the nervous phase of gastric secretion is dependent on the presence of the hormone, gastrin. Other instances of interdependence of nervous and humoral mechanisms are discussed.

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## THE NOCTURNAL GASTRIC SECRETION IN PATIENTS WITH GASTRIC CARCINOMA: A COMPARISON WITH NORMAL INDIVIDUALS AND PATIENTS WITH DUODENAL ULCER AND WITH GASTRIC ULCER\*

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### INTRODUCTION

The results of studies on the continuous nocturnal gastric secretion in patients with gastric carcinoma have been summarized in a previous publication<sup>1</sup>. Although the number of patients was relatively small certain trends were noted. The series now has been increased sufficiently to permit definite conclusions. The purpose of the present paper is to describe in detail the periodicity and variability of the nocturnal gastric secretion in such patients and to compare them with normal subjects and with patients having either duodenal ulcer or benign gastric ulcer. To our knowledge, a similar study has not been presented heretofore.

### METHODS

The methods employed and the criteria used in selection of subjects have been described previously<sup>1,2,3,4</sup>. The conditions of study were identical in all. Fifty-five studies were obtained in 28 patients with proven carcinoma of the stomach. Microscopic evidence of the nature of the lesion was obtained in all cases except one, in the latter the nature of the lesion was established by x-ray examination, gastroscopy, and the clinical course.

### RESULTS

#### *Total Night Secretion*

*Volume:* The individual volumes of the total night secretion ranged from 105 cc. to 1412 cc., averaging 483 cc. (Tables I and II). The volume was less than 1000 cc. in 92 per cent of the studies. It ranged between 100 and 400 cc. in approximately 66 per cent (Fig. 1). Variations were observed not only among individuals, but also in the same person on different nights. The individual variation for the group averaged 25 per cent.

*Free acidity:* The free acidity of the total night secretion ranged from 0 to 51 clinical units, averaging 14 (Tables I and II). It was less than 20 clinical units in 76 per cent. Anacidity in the total night secretion was observed in 38 per cent of the studies (Fig. 2).

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TABLE I

*The 12-hour continuous nocturnal gastric secretion in patients with gastric carcinoma  
(8:30 P.M. to 8:30 A.M.)*

NAME UNIT #	VOLUME	FREE ACID	FREE HCl
	<i>cc.</i>	<i>Cl. units</i>	<i>mg.</i>
H. P. #379526	457	0	0
	627	32	720
	320	13	149
J. V. P. #348596	588	7	150
	464	8	143
O. R. #394483	587	5	113
J. W. #392940	1243	0	0
	377	0	0
B. K. #375830	298	0	0
	571	0	0
W. K. #377081	518	0	0
	355	0	0
F. Z. #383018	586	14	304
	332	9	110
	296	1	2
	453	3	58
E. Z. #392713	205	2	11
	295	1	8
J. L. #401432	375	7	87
	311	0	0
J. C. #392945	259	14	131
	290	13	137
	322	1	5
A. E. #388237	446	0	0
	472	0	0
T. D. #119556	288	0	0
M. C. #430008	820	38	1131
	761	47	1300
E. P. #298283	105	9	36
	336	4	49
	167	0	0
A. K. #426638	452	23	373
	378	30	408

TABLE I—*Concluded*

NAME UNIT #	VOLUME	FREE ACID	FREE HCl
	cc.	Cl. units	mg.
P. S. #405266	424	0	0
	492	0	0
J. S. #179336	306	2	24
M. M. #411009	205	0	4
I. S. #417483	1312	20	962
	1182	4	190
N. B. #420898	543	46	912
G. McC. #418968	703	33	853
	687	51	1256
B. E. #422219	276	16	158
F. W. #25110	542	1	20
	488	14	253
F. B. #426615	279	0	0
	306	0	0
S. W. #426528	226	0	0
	164	0	0
H. T. #429424	1412	39	2007
	895	41	1328
F. K. #428634	193	6	42
	231	4	30
R. J. #430864	785	0	0
	560	0	0

TABLE II

*The average volume, free acidity and Mg free HCl in the 12-hour nocturnal gastric secretion in normal individuals and in patients with duodenal ulcer, gastric ulcer and gastric carcinoma*

	VOLUME	FREE ACID	FREE HCl
	cc.	Cl. units	mg.
Normal	581	29	661
Duodenal ulcer	1004	61	2242
Gastric ulcer	600	21	454
Gastric carcinoma	483	14	245

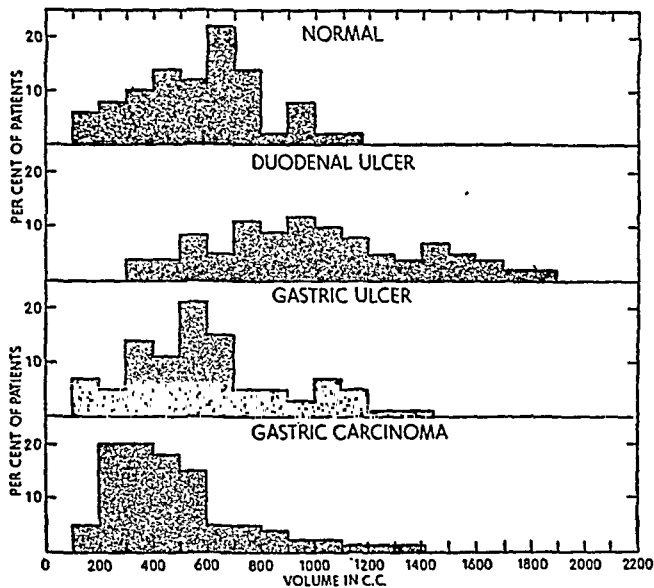


FIG. 1. DISTRIBUTION OF TOTAL VOLUME OF 12-HOUR NOCTURNAL GASTRIC SECRETION

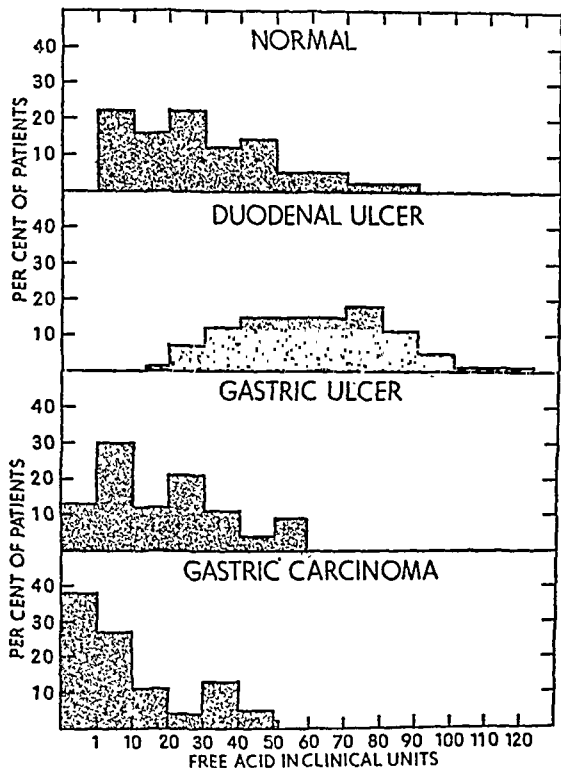


FIG. 2. DISTRIBUTION OF FREE HCl OF 12-HOUR NOCTURNAL GASTRIC SECRETION

The free acidity varied in the same individual on different nights. However, this variation as a rule was insignificant, usually not exceeding 10 clinical units.  
*Mg. Free HCl:* The output of free HCl for the 12-hour period averaged 245

mg., the range being 0 to 2007 mg. (Tables I and II). It was less than 1000 mg. in 91 per cent of the studies and below 500 mg. in 80 per cent. Of the latter, anacidity was present in 45 per cent and less than 200 mg. were obtained in 89 per cent. The acid output exceeded 2000 mg. in only 2 per cent (Fig. 3).

Individuals secreting a small amount of acid in one night in the vast majority of instances produced a small amount on successive nights; a similar constancy existed for patients with a high secretory rate. This correlation was observed also for both the volume and free acid concentration.

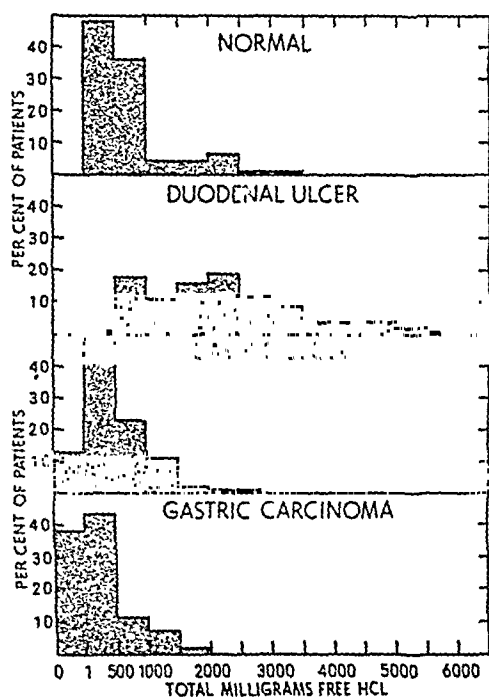


FIG. 3. DISTRIBUTION OF TOTAL MILLIGRAMS FREE HCL IN 12-HOUR NOCTURNAL GASTRIC SECRETION

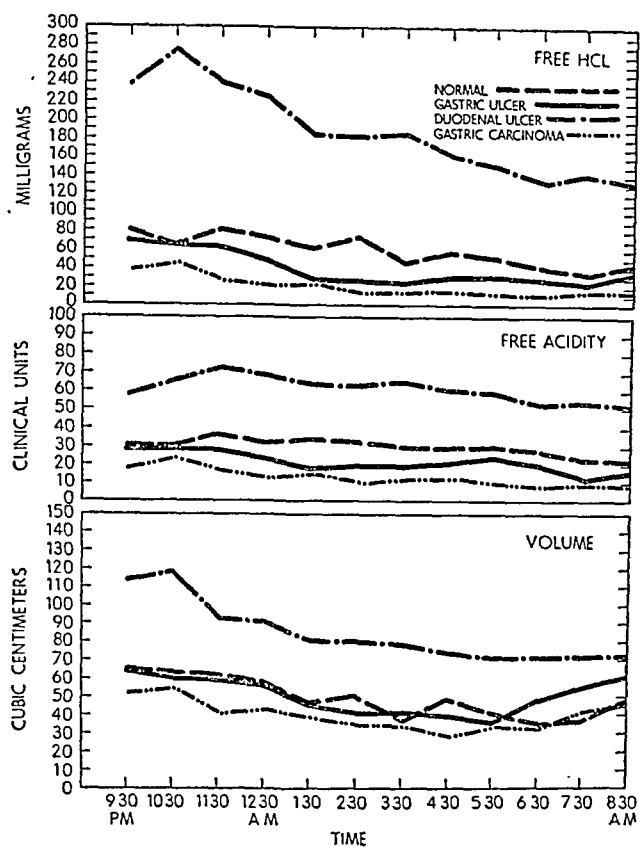
### *The Hourly Variation in Nocturnal Gastric Secretion*

**Volume:** The gastric secretion was as a rule continuous; there rarely was a lack of gastric juice for one hour. The highest hourly volume was 190 cc.; the average was 40 cc.

The *average* hourly secretion decreased gradually until 4:30 A.M.; there tended to be gradual increase during the last four hours (Fig. 4). There was no significant difference between the average volume for the first half of the night and the last half (Table III).

There was a marked variation in the periodicity of the night secretion not only between subjects, but also in the same individual. The rate of secretion was not constant from hour to hour. The hourly variation for the entire group averaged approximately 33 per cent. The maximum hourly volume may occur

at any time during the night. In this series, the maximum output of gastric juice occurred prior to 2:30 A.M. in 65 per cent of the studies. It was not uncommon for an individual to maintain a constantly low secretory rate for



4. NOCTURNAL GASTRIC SECRETION AVERAGE HOURLY OUTPUT

TABLE III

The average volume, free acidity and milligrams of free hydrochloric acid secreted during quarterly periods of the night in patients with gastric carcinoma

TIME	VOLUME	FREE ACIDITY	FREE HCl
	cc.	Cl. units	mg.
8:30 P.M. - 11:30 P.M.	145	20	107
11:30 P.M. - 2:30 A.M.	117	14	58
2:30 A.M. - 5:30 A.M.	99	12	42
5:30 A.M. - 8:30 A.M.	122	8	38

several consecutive hours (i.e. less than 30 cc. per hour for 8-10 hours). Relatively persistent hypersecretion was seen in only one individual.

Two representative patterns are shown in Fig. 5. Differing patterns were also obtained in the same individual when more than one study was made; a typical example is shown in Fig. 6.

*Free Acid:* The secretion of acid, in contrast to the volume, was not continuous in all cases. Acid was secreted continuously throughout the night in only four studies (three patients); anacidity for two consecutive hours or more was noted in the remainder. Eight patients, who were studied more than once had persistent achlorhydria throughout the night on each occasion.

The highest free acidity in one hour was 70 clinical units; the hourly value for the entire group averaged 13 clinical units. The free acidity was persistently below 15 clinical units throughout the night in 50 per cent of the studies. In no instance was it persistently greater than 25 clinical units throughout the night. In many patients the free acidity under fasting conditions for some

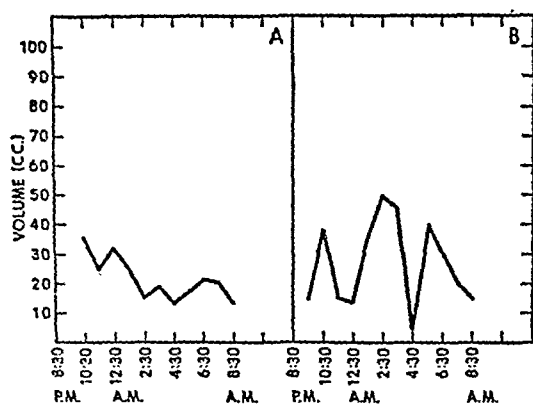


FIG. 5

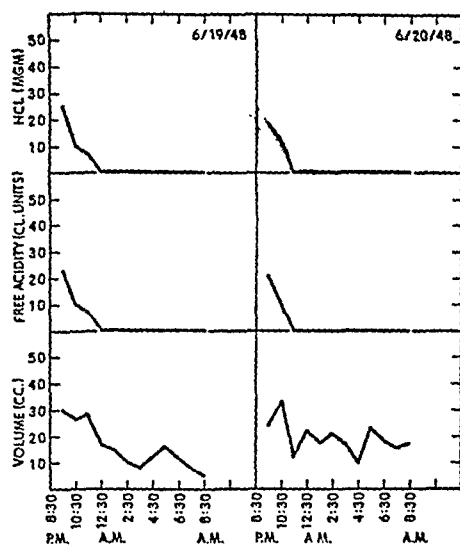


FIG. 6

FIG. 5. REPRESENTATIVE PATTERNS IN THE HOURLY VOLUME OF GASTRIC SECRETION DURING THE NIGHT IN PATIENTS WITH GASTRIC CARCINOMA

FIG. 6. PATTERNS OF THE HOURLY VOLUME, FREE ACIDITY AND OUTPUT OF FREE HYDROCHLORIC ACID IN THE SAME PATIENT ON SUCCESSIVE NIGHTS (GASTRIC CARCINOMA)

hourly specimens not infrequently equalled that produced in response to histamine.

There was a gradual decrease in the average hourly concentration of acid as the night progressed (Fig. 4). The average free acidity was greater for the first half of the night than for the last half (Table III).

Representative individual patterns are shown in Fig. 7. As with the volume, there was a marked variation from one individual to another. In general the maximum concentration of acid may occur at any hour of the night. In all of the studies except six it occurred before 11:30 P.M.

Unlike the volume, varying patterns were noted infrequently in the same individual on different nights. An example is shown in Fig. 6.

*Milligrams of Free Hydrochloric Acid:* The average hourly output of free hy-



drochloric acid gradually decreased during the night (Fig. 4). The amount secreted during the first half of the night was significantly greater than that produced during the second half (Table III).

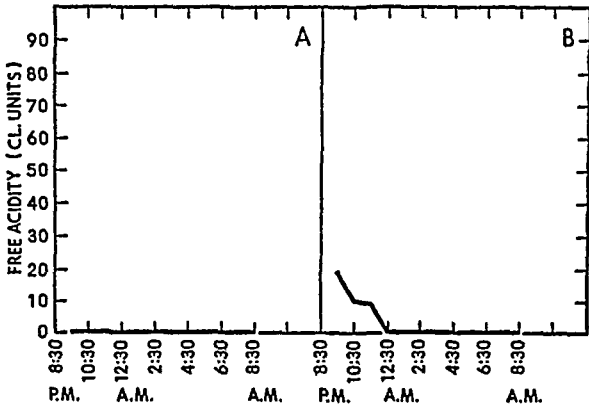


FIG. 7. REPRESENTATIVE PATTERNS IN THE HOURLY FREE ACIDITY OF THE NOCTURNAL GASTRIC SECRETION IN PATIENTS WITH GASTRIC CARCINOMA

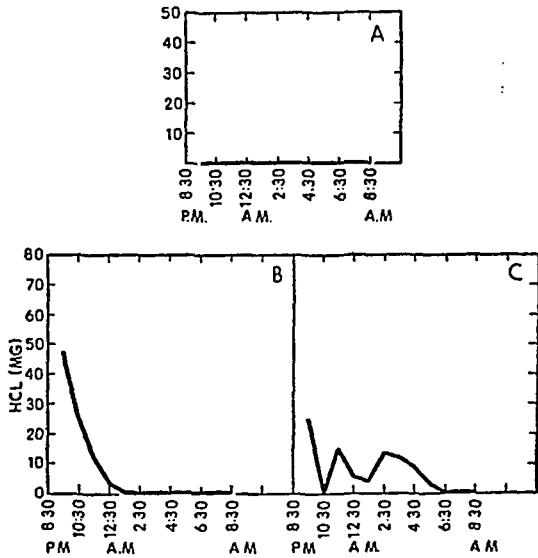


FIG. 8. REPRESENTATIVE PATTERN IN THE HOURLY OUTPUT OF HYDROCHLORIC ACID DURING THE NIGHT IN PATIENTS WITH GASTRIC CARCINOMA

Even though the rate of secretion of acid was not constant, the fluctuation from hour to hour was not great. An individual with a low secretory rate in the early evening maintained this low secretory rate throughout the night, or more frequently ceased secreting acid entirely after the first 2-3 hours. The maximum secretion of acid in all patients except four occurred before 1:30 A.M. A progressively increasing hourly output of acid was not observed in this series. In 75 per cent of the studies no free acid was obtained after 3:30 A.M. The amount of acid persistently exceeded 50 mg. throughout the night in only one

individual. The largest individual quantity of acid secreted in one hour was 500 mg.; the hourly output for the entire group averaged 20 mg. Fig. 8 shows representative patterns obtained.

Varying patterns were noted infrequently in the same individual on successive nights (Fig. 6). This is probably due to the fact that the majority of patients of this group do not secrete free HCl as the night progresses. It is of interest that the majority of individuals with long periods of anacidity during one night manifested similar periods of anacidity on successive nights.

*Comparison with Normal Individuals and with patients with Duodenal Ulcer and Gastric Ulcer*

This study indicates significant differences in the basal gastric secretion between patients with gastric carcinoma and normal individuals, and patients with duodenal ulcer or benign gastric ulcer.\* As one would expect there is some overlapping.

The average 12-hour volume is lowest in patients with gastric carcinoma (Table II). Occasionally one encounters a patient with gastric carcinoma who produces a relatively high volume. In only 8 per cent of the studies in this series was the volume greater than 1000 cc. (Fig. 1); the highest 1412 cc. In patients with duodenal ulcer, the average volume was 1000 cc. (Table II), approximately twice that for gastric carcinoma, and volumes of 1400 cc. and higher were frequently seen. Although there is no great difference between the average volumes of normal individuals, benign gastric ulcer patients and gastric carcinoma patients (Table II), an analysis of the data reveals that the majority of the latter secrete lower volumes than the former. Volumes less than 500 cc. were seen in 63 per cent of the patients with carcinoma; in contrast to only 38 per cent of the normal individuals and in 37 per cent of the patients with benign gastric ulcer (Fig. 1).

Gastric secretion was continuous in all four groups. Rarely was there an absence of secretion for as long as one hour. In all subjects studied, the rate of secretion varied from hour to hour. In duodenal ulcer patients it was not uncommon for an individual to maintain a constantly high secretory rate for several consecutive hours, this was rarely seen in patients with gastric carcinoma, normal individuals or benign gastric ulcer. In all four groups, the maximum volume occurred prior to 2:30 A.M. in the majority of instances. Although there was a tendency for the average hourly secretion to decrease gradually during the night in all four groups, the secretory rate in the duodenal ulcer series constantly remained at a distinctly higher level, and that for gastric carcinoma at a distinctly lower level (Fig. 4).

\* For complete data of normal individuals and patients with duodenal and gastric ulcers see references 1, 2, 3, and 4.

The free acidity of the total night secretion varied in the four groups studied (Table II). The average was lowest in patients with carcinoma. Fig. 2 shows that the majority of patients in this group had a lower free acidity than normal individuals, and patients with gastric or duodenal ulcer. It was below 10 clinical units in 69 per cent of the carcinoma patients as compared with 47 per cent with gastric ulcer, 24 per cent for normal individuals and none with duodenal ulcer.

The individual fluctuations in concentration of acid were greater in both the normal subjects and duodenal ulcer patients than in the gastric carcinoma group. Variations larger than 5 clinical units were observed in only eleven individuals of the latter series; a similar number was obtained in patients with benign gastric ulcer. Except for the normal group, the majority of patients with a high concentration of acid on one night manifested a high concentration on successive nights. A similar constancy was observed in patients with a low concentration.

Whereas in patients with duodenal ulcer the secretion of acid was continuous in all studies except three, it was not continuous in the vast majority of normal individuals and patients with either gastric carcinoma or gastric ulcer. Periods of anacidity for one or more hours were noted in 93 per cent of the gastric carcinoma studies, in 70 per cent of the normals, and in 81 per cent of the gastric ulcer group.

The concentration of acid was persistently below 50 clinical units throughout the night in 94 per cent of the gastric carcinoma studies, in 71 per cent of the gastric ulcer patients, in 44 per cent of normal group, and 35 per cent of the duodenal ulcer studies. On the other hand, in none of the gastric carcinoma or gastric ulcer patients was it persistently greater than 50 clinical units, whereas values higher than 50 were noted in 6 per cent of the normal group and in 35 per cent of the duodenal ulcer series.

The average hourly concentration is highest in patients with duodenal ulcer and lowest in gastric carcinoma patients (Fig. 4). In all, the maximum hourly concentration in the vast majority of instances occurred prior to 2:30 A.M. In general, the concentration gradually decreased during the night in the same individual. The patterns varied from one individual to another, but in patients with carcinoma the patterns varied very little in the same individual on different nights, a finding not encountered in the other three groups studied.

The amount of free HCl for the 12-hour period was lowest in patients with gastric carcinoma, the average being 245 mg.; the average for the normal group was 661 mg., for patients with benign gastric ulcer 454 mg., and for patients with duodenal ulcer 2,242 mg. (Table II). Although there was some overlap in the distribution, the differences are statistically significant (Fig. 3). In the carcinoma group, it was less than 1000 mg. in 91 per cent of the studies

and below 500 mg. in 80 per cent. Of the latter, it was less than 200 mg. in 89 per cent and anacidity was present in 45 per cent. In the gastric ulcer group it was less than 1000 mg. in 85 per cent of the studies and below 500 mg. in approximately two-thirds. Of the latter it was less than 200 in 57 per cent and anacidity was present in 22 per cent. In normal individuals, the output was less than 1000 mg. in 84 per cent of the studies and below 500 in 50 per cent. Approximately two-thirds of the latter were below 200 mg., no individual having complete anacidity. In contrast, among patients with duodenal ulcer an output less than 500 mg. was noted in only one instance. It exceeded 1000 mg. in 81 per cent and 2000 mg. in more than 50 per cent.

There is a gradual decrease in the average hourly secretion of free hydrochloric acid in all four groups studied (Fig. 4). The hourly secretion averaged 20 mg. in gastric carcinoma patients, 38 mg. in gastric ulcer patients, 55 in normal individuals and 187 mg. in patients with duodenal ulcer. The amount

TABLE IV  
*Nocturnal gastric secretion hourly output of free hydrochloric acid*

	PER CENT OF STUDIES			
	Anacidity	Persistently below 50 mg.	Persistently greater than 50 mg.	Persistently greater than 100 mg.
Normal . . . . .	0	28	12	4
Duodenal ulcer . . . . .	0	0	63	32
Gastric ulcer . . . . .	13	32	2	0
Gastric carcinoma . . . . .	38	64	2	0

of acid was persistently greater than 50 mg. throughout the night in only one individual with carcinoma. This was not uncommon in both normal individuals and patients with duodenal ulcer, but rarely seen in patients with benign gastric ulcer. On the other hand, the hourly output of acid was persistently below 50 mg. throughout the night in 64 per cent of the carcinoma patients, in 32 per cent of the gastric ulcer patients, in 28 per cent of the normal individuals, and in none of the patients with duodenal ulcer (Table IV). Free acid was not obtained after 6:30 A.M. in 78 per cent of patients with gastric carcinoma, as compared with 55 per cent in patients with gastric ulcer, 18 per cent of the normal group; anacidity after 6:30 A.M. was never observed in patients with duodenal ulcer.

The rate of secretion in the same individual was not constant in all four groups. In the majority of individuals the maximum hourly secretion of hydrochloric acid occurred prior to 2:30 A.M. Varying patterns were present from individual to individual and also in the same individual on different nights. As a rule, however, in all subjects studied, an individual with a high secretion

on one night, manifested a relatively high secretion of acid on successive nights. This also held true for subjects with a relatively low secretion rate.

### *Comment*

This study demonstrates significant differences between the basal gastric secretion of normal individuals and patients with gastric carcinoma, benign gastric ulcer, and duodenal ulcer. The question that immediately arises is "What are the factors involved in such marked differences"? At present there is no answer; however, evidence accumulated during the past several years indicates that there are anatomical and physiological differences between the four groups.

Meyers<sup>5</sup> in a recent study showed that the number of parietal cells in the stomach is greater in patients with duodenal ulcer than in those with either benign gastric ulcer or gastric carcinoma. The smallest number of cells were found in patients with carcinoma. Similar figures are not available for normal individuals. The results obtained by Meyer coincide very nicely with the results of this study. The secretion of acid was highest in patients with duodenal ulcer and lowest in gastric carcinoma. Thus, an anatomical correlation seems to have been established.

Also, during the past several years evidence has accumulated that increased vagal activity is present in patients with duodenal ulcer. It has been shown repeatedly that the basal secretion is markedly reduced following successful bilateral vagotomy. The data obtained by Thornton, Storer, and Dragstedt<sup>6</sup> and by Clark, Storer, and Dragstedt<sup>7</sup> are of particular interest. Their post-vagotomy studies were made employing the same test meal at 5:30 P.M. and aspiration of the stomach during the same period of the night. Their data demonstrate that the night secretion is reduced to normal or subnormal values (i.e. to values obtained in the majority of normal individuals in the present series) after presumably complete vagotomy. In our opinion, this finding, combined with the fact that the secretion of acid is three and half times greater in patients with duodenal ulcer than normal individuals is strong evidence in favor of the presence of increased vagal tonicity as the most important cause of hypersecretion in patients with duodenal ulcer. Whether or not this state is due to direct stimulation of the parietal cells by the vagus nerves or indirectly by the liberation of acetyl-choline which conditions the cell to respond to a greater degree to various chemical substances, as postulated by Grossman<sup>8</sup>, remains open to question.

The question may also arise that the increased secretion in duodenal ulcer may, in some way, be due to the presence of an active ulcer crater. Night secretion studies recently made by us on 13 duodenal ulcer patients during the presence of an active ulcer and also at varying periods after healing indicate

that the amount and character of the gastric secretion does not significantly change with healing. The average volume and acid secreted after healing of the ulcer is higher than that found in normal individuals.<sup>16</sup>

In patients with gastric ulcer a different situation exists, for the evidence to date indicates that increased vagal tonicity is not present in the vast majority of this group. The average output of acid under basal conditions is less than that found in healthy normal individuals. Apparently some reduction does occur after bilateral vagotomy in this group, but it is so slight as to be of questionable significance. It can be safely assumed that increased vagal tone does not exist in patients with gastric carcinoma since their basal secretion is usually lower than that of patients with benign gastric ulcer. Furthermore, in both groups studied long periods of anacidity are frequently seen.

To our knowledge similar studies on the *continuous* 12-hour nocturnal gastric secretion in the four groups compared above have not been reported heretofore. In the studies made by Henning and Norpoth<sup>9</sup>, Winkelstein<sup>10</sup>, Val Dez<sup>11</sup>, Hellebrandt<sup>12</sup>, and Voegtlin<sup>13</sup> "*periodic*" sampling of the night secretion was employed.

Thornton, Storer and Dragstedt<sup>6</sup>, and Clarke, Storer, and Dragstedt<sup>7</sup> measured the continuous night secretion in patients with duodenal ulcer, carcinoma of the stomach, cholelithiasis and chronic cholecystitis and in a miscellaneous group of patients having pathology other than ulcer. No similar control studies were made in healthy normal individuals. The authors rightly point out that their non-ulcer patients do not constitute an ideal control group because of the presence of disease other than ulcer<sup>7</sup>. It is of interest to note, however, that in these studies patients with duodenal ulcer had a greater secretion than those with gastric carcinoma; a finding which is in agreement with the present observations.

Sandweiss et al.<sup>14, 15</sup> also studied the continuous night secretion (12:00 midnight to 7:00 A.M.) in normal individuals and duodenal ulcer. The results obtained by us and by Sandweiss are not in agreement. An attempt to explain the possible reasons for this disagreement has been made in a previous publication<sup>3</sup>.

#### CONCLUSIONS

1. The secretion of gastric juice in patients with gastric carcinoma is apparently continuous; although the secretion of hydrochloric acid is not continuous.
2. The volume of secretion and output of acid are usually higher during the first half of the night than during the last half.
3. Although individual variations exist, a patient with a low secretion on one night, in the majority of instances, has a low secretion on successive nights; a similar correlation is present in patients with a high secretory rate.
4. The rate of gastric secretion is not constant.

5. The volume, concentration and output of acid in the nocturnal gastric secretion are lower in patients with gastric carcinoma than in normal healthy individuals or in patients having either duodenal or benign gastric ulcer.

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## THE INFLUENCE OF SMOKING UPON THE MANAGEMENT OF THE PEPTIC ULCER PATIENT

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### INTRODUCTION

During an investigation<sup>1</sup> of antacids for the treatment of the ambulatory patient with peptic ulcer, (it was noted that tobacco smoking played a considerable role in the evaluation of these medications.) (An attempt was therefore made to determine what relationship tobacco smoking has to the symptoms and course of the peptic ulcer syndrome.) It is the purpose of this report to consider two phases of the problem: (1) the influence of tobacco smoking on the management of the peptic ulcer patient as measured by the effectiveness of antacid therapy and the incidence of acute exacerbations, and (2) the influence of smoking processed or partially denicotinized tobacco upon the course of the peptic ulcer patient.

### MANAGEMENT OF THE PEPTIC ULCER PATIENT

All patients were ambulatory and presented roentgenologic evidence of duodenal or gastric ulceration. None of the patients had a history of hemorrhage. Six patients had previous surgical interventions, such as establishment of a gastroenterostomy or repair of a perforated ulcer. In all, there were one hundred and eight patients. Fifty-six, or 52 per cent, of the patients were smokers, with forty-three of the patients (40 per cent) continuing to smoke throughout the investigation. Twenty-six (24 per cent) gave a history of smoking but discontinued the use of tobacco of their own accord when first seeking treatment. However, half of these patients resumed smoking when clinical improvement occurred, so that they were observed under both conditions. Thirty-nine (36 per cent) of the patients were non-smokers. The incidence of duodenal ulceration for smokers and non-smokers was 92.8 per cent and 89.5 per cent respectively, while that for gastric ulceration was 7.2 and 10.2 respectively.

All patients were members of the original group of patients reported previously<sup>1</sup> for antacid evaluation and accordingly followed the same regime. (Patients were seen in the clinic at intervals of one to four weeks, at which time they were carefully questioned as to their smoking habits and the occurrence of abdominal pain, eructations, heartburn, nausea, vomiting, abdominal distension and bowel habits.) Although the majority of patients had more than one antacid, the influence of smoking upon the adequacy of treatment was



considered for only the most effective of the medications. With the exception of an occasional patient not attending the clinic at the appointed visit, the majority of patients were on continuous antacid therapy for the entire period of observation, which averaged 60 weeks. Any break in therapy, either to adjust antacid medication or because of failure to keep an appointment, was considered as a new trial of observation.

#### I. RESULTS OF ANTACID THERAPY AS INFLUENCED BY SMOKING

✓ The influence of smoking was considered in terms of the ability of the patient to respond to an antacid. Four groupings of effectiveness of therapy were made: (1) an excellent clinical response(+++) with complete alleviation of the symptoms, maintenance of well-being and absence of acute exacerbations of symptoms.

(2) a moderate response(++) with almost complete relief of symptoms. These would persist to a lessened degree, occurring periodically, but would not be too distressing. An acute exacerbation of symptoms may have occurred but this would be mild and of short duration.

(3) a slight response(+) to antacid therapy where the symptomatic improvement did not in any way alter the status of the underlying disease. The relief would usually be of a temporary nature. Exacerbations would be moderately severe and of moderate duration.

(4) in spite of antacid therapy, the patient would have no relief of symptoms, or the relief would be insufficient to forestall a progressive increase in the severity of the disease(n-w). Exacerbations would be frequent, severe, and of long duration.

The results are summarized in Table I. Of the patients who continued to smoke, a satisfactory clinical response to antacid therapy was obtained in 46.8 per cent of the trials. The others had no change in their status or actually became worse during the period of observation. ✓ On the other hand, the non-smokers presented satisfactory improvement in 85 per cent of the trials. In only six patients was the response considered to be inadequate. The incidences of acute exacerbations during the period of antacid therapy reveals very strikingly the influence of smoking upon the course of the peptic ulcer syndrome. ✓ The patients who smoked presented acute exacerbations in thirty-four or 53 per cent of the trials, in contrast to the non-smokers who had exacerbations in 17.5 per cent of the trials.

The group of 26 patients who stopped smoking of their own accord before seeking treatment is of particular interest. In every case there was a satisfactory clinical response to antacid therapy. The incidence of exacerbations which were usually of mild character was 11.5 per cent. Of the 13 patients who resumed smoking after clinical improvement occurred, 11 showed an im-

mediate regression of their disease, with intensified symptoms and acute exacerbations.

## II. THE COURSE OF PEPTIC ULCER AS INFLUENCED BY SMOKING PROCESSED TOBACCO

Since the cessation of smoking appears to be an important consideration in the management of a patient with peptic ulcer, the question arose as to what

TABLE I  
*Influence of smoking upon effectiveness of antacid therapy*

STATUS	DIAGNOSIS*	NO. OF POINTS	NO. OF TRIALS	EFFECTIVENESS OF ANTACIDS†								EXACERBATIONS	
				+++		++		+		N-W			
				No. of trials	Per cent	No. of trials	Per cent	No. of trials	Per cent	No. of trials	Per cent	No. of trials	Per cent
Smokers	DU	47	55	10	18.1	14	25.4	15	27.3	16	29.1	31	56.4
	GU	3	3	2		1							
	DU (Perf)	3	3	1		1		1				2	
	DU (GE)	2	2			1		1				1	
	GU (GE)	1	1					1					
	Total	56	64	13	20.3	17	26.5	18	28.1	16	25.0	34	53.1
Smoked	DU	25	25	16	64.0	9	36.0					3	12.0
	GU (Perf)	1	1	1									
	Total	26	26	17	65.4	9	34.6					3	11.5
Non-smokers	DU	32	33	19	57.6	9	27.3	1	3.0	4	12.1	7	21.2
	DU & GU	2	2	2									
	GU	4	4	2		1		1					
	DU (Perf)	1	1			1							
	Total	39	40	23	57.5	11	27.5	2	5.0	4	10.0	7	17.5
Total of non-smokers.....		65	66	40	60.6	20	30.3	2	3.0	4	6.1	10	15.1

\* DU—Duodenal ulcer; GU—Gastric ulcer; Perf.—perforated; GE—gastro-enterostomy.

† +++—excellent; ++—moderate; +—slight; N-W—no effect or patient worse.

should be done with patients who cannot deprive themselves of the use of tobacco. It was thought that the use of processed or "denicotinized" tobacco may have some value for such patients. For purposes of the study, patients were chosen who had persistent symptoms from their peptic ulcer and whose response to antacid and dietary treatment was not satisfactory so long as they continued to smoke. Of the 28 patients selected, 26 were males. Twenty-four patients presented an uncomplicated duodenal ulcer, as demonstrated by roentgenologic examination. Four patients had previous surgical intervention, with three possessing a gastroenterostomy, while the fourth had

a repair of a perforated duodenal ulcer. All patients were ambulatory and were observed for months or years prior to inclusion in this phase of the investigation, so that their response to antacid therapy, as influenced by smoking, was well-known. Only six, or approximately 21 per cent, of these patients presented any appreciable improvement to antacid therapy. The majority had only slight relief from the symptoms of which they complained, while approximately 29 per cent of the patients had either no response or became progressively worse, with repeated, severe exacerbations. The incidence of exacerbations for the entire group of patients was 53.5 per cent.

TABLE II  
*Influence of "processed" and regular tobacco upon the effectiveness of antacids*

STATUS	NUMBER OF PATIENTS	EFFECTIVENESS OF ANTACIDS†								EXACERBATIONS	
		+++		++		+		N-W		No. of Patients	Per cent
		No. of Patients	Per cent	No. of Patients	Per cent	No. of Patients	Per cent	No. of Patients	Per cent		
1. Control—smoking Regular Tobacco.....	28	0		6	21.4	14	50.0	8	28.6	15	53.5
2. Smoking—"Processed" Tobacco.....	28	11	39.3	11	39.3	4	14.3	2	6.9	8	28.6
3. Smoking—"Camouflaged" (Regular) Tobacco.....	10	1	10.0	4	40.0	0	—	5	50.0	5	50.0
4. Smoking—Regular (Popular Blend) Tobacco.....	11	0	—	2	18.1	4	36.3	5	45.4	7	63.6
5. Smoking—"Camouflaged" or Popular Blend Tobacco.	18*	0	—	4	22.2	5	27.7	9	50.0	12	66.6
6. Retrial—Smoking "Processed" Tobacco.....	13	5	38.4	4	30.8	2	15.3	2	15.3	4	30.8

\* Three patients were observed while smoking both "camouflaged" and regular popular blend tobacco.

† +++—excellent; ++—moderate; +—slight; N-W—no effect or patient worse.

The patients were advised to smoke only the processed or "denicotinized" cigarettes which were supplied\* at each clinic visit in sufficient quantities to last until the next appointment. It should be emphasized that these cigarettes are not completely denicotinized. Their nicotine content averaged 0.85 per cent\* as compared with 1.5 to 2.5 per cent in standard brand cigarettes. It may be readily appreciated that the decreased content of nicotine can easily be compensated for by increasing the number of cigarettes smoked. For this reason, and because it is not entirely clear that nicotine is the only responsible

\* This study was made possible by the fullest cooperation and generous supplies of Sano cigarettes by the Fleming-Hall Company, Incorporated, New York, New York. The nicotine content of various lots of these cigarettes were tested by Stillwell and Gladding, analytical chemists, from 1940 to 1947 inclusive and averaged 0.85%.

factor for observed clinical and pharmacological effects, it is best to use the term "processed" cigarettes rather than "denicotinized" cigarettes.

The patients were followed according to the regime described in the first phase of the investigation. The average duration of observation was 36 weeks, with a range from 8 to 176 weeks. The results are summarized in Table II. Of the 28 patients, 22 (78.6 per cent) showed immediate improvement, with either excellent or moderate response to antacid therapy. Eleven of these had complete subsidence of all symptoms. The outstanding effect was the disappearance of heartburn within a few days, followed by decrease or complete cessation of epigastric pain within a few weeks. Of the patients presenting moderate improvement, the symptoms persisted but were of a milder character and were not distressing to the patient. In four patients the response was insignificant, while two patients either became worse or had no change in their condition. Of the latter six patients, two possessed a gastroenterostomy, and two subsequently required surgery. Of the entire group of patients exacerbations were noted in eight, or 28.6 per cent.

Even though the results appear conclusive, the study was not entirely satisfactory because of the possibility of the patient reporting a favorable response in order to obtain free cigarettes. To circumvent this, the study was continued according to the following phases: of the original group of 22 patients who showed a satisfactory response to antacids, 18 patients were subsequently observed for the effects of re-institution of unprocessed or regular tobacco. Ten of these patients were supplied with cigarettes of unprocessed tobacco, without their knowledge of the change. Tobacco of approximately twice the nicotine content was especially prepared in the same cigarette wrappings and packages as the processed cigarettes. From the external appearance of the cigarettes it was impossible to distinguish which was which. Six of the patients who smoked this camouflaged cigarette became worse and redeveloped their symptoms. Two of the patients had a severe exacerbation necessitating hospitalization. Another group of patients resumed smoking the brand of tobacco previously used. In addition, three patients who were smoking camouflaged cigarettes, also returned to their original brand, thus making eleven of such patients available for analysis. Eight of these patients became clinically worse. It is of interest to note that the effectiveness of antacids in patients who smoked either the camouflaged or regular tobacco diminishes and becomes identical with the control group. The incidence of exacerbation increases to the level observed in the control group.

It was possible to reinstitute the use of processed tobacco in 13 of these 18 patients. Eight of the patients had a restoration of a favorable response. The effectiveness of antacids and incidence of exacerbation for the entire group of 13 patients were identical with the earlier results.

## DISCUSSION

(Whether or not tobacco or its constituents can be an etiological factor in the production of gastrointestinal disease has been the subject of considerable literature.) However, no evidence other than a dogmatic statement is presented by the authors. (Thus, Hurst and Stewart<sup>2</sup> state "that most people with duodenal ulcer have smoked excessively for many years.") (Lichint<sup>3</sup> believes that tobacco may be an etiological factor in gastric neuroses,) in disturbances of secretory functions, in gastritis, ulcers, and even cancer. (Wagner<sup>4</sup> insists that all the subjective and roentgenologic signs of duodenal ulcer can be produced by excessive use of tobacco.) Ochsner, Gage, and Hasoi<sup>5</sup> stress the causal relation of tobacco to peptic ulcer. This view is also held by others.<sup>6</sup> (Bennett<sup>7</sup> says, "It is rare to see a duodenal ulcer in a non-smoker.") (Hurst and Stewart<sup>2</sup> and Bandel<sup>8</sup> make the same claim.) (The argument<sup>9</sup> is offered that there is a causal relationship between the parallel increase of peptic ulcer and the incidence of smoking in both world wars.) On the other hand, Barnett<sup>10</sup> reported that the incidence of smokers, 75 per cent, in a control group was approximately the same as that, 80 per cent, found in patients with peptic ulcer. Furthermore, Trowell<sup>11</sup> found that men suffering from chronic duodenal ulcer do not on the average smoke more tobacco than normal males. However, the former have almost double the number of inhalers. This is of doubtful significance in the light of the findings of Pierce<sup>12</sup> which will be commented upon later. In our own series of patients, 36 per cent were non-smokers. Of those who smoked, with the exception of one patient who smoked as much as 40 to 60 cigarettes daily, the amount of smoking appeared no higher than in the general population. In fact, many of our patients were in economic difficulties and limited the extent of their smoking to less than ten cigarettes daily. These findings are in accord with the idea that tobacco smoking is not an etiological factor in the causation of peptic ulcer.

(Another approach to the subject is the immunologic experiments of Sulzberger<sup>13</sup> who claims that an organ or part of an organ may be sensitized to an allergen, in this case to tobacco.) (This sensitized organ would then behave in a way to produce an organic disease, such as peptic ulcer.) It is difficult to refute this type of argument when Sulzberger admits that a negative skin test to tobacco does not rule out "clinical evidence of tobacco hypersensitivity.") (Harkavy<sup>14</sup> noted that in 60 cases of gastroduodenal ulcer, 16, or 26 per cent, were sensitive to tobacco.) However, Ehrenfeld and Sturtevant<sup>15</sup> were unable to demonstrate sensitivity to a tobacco extract in a similar group of patients.

Although there isn't any proof that tobacco may be a causative factor in organic gastrointestinal disease, there is some evidence that tobacco smoking may result in functional disturbances which may simulate organic disease or aggravate a pre-existing functional or organic disease.) Friedrich<sup>16</sup> reports

that in a group of patients who were operated upon for peptic ulcer, recurrence of their symptoms was noted in 50 per cent of 34 patients, while in 44 patients, who had stopped smoking, only six, or 13 per cent, had recurring mild symptoms. The detrimental effects of smoking were noted particularly in patients with a gastroenterostomy. In 14 patients all but four relapsed when smoking<sup>1</sup> was continued, while in 30 patients who reduced or stopped smoking there were only four relapses. (Gray<sup>17</sup> reports the most complete analysis of 300 patients with functional gastric disturbances, and 100 patients with organic disease. Of the functional group, the largest number presented heartburn as the only complaint. The majority of patients with functional disturbances had alleviation or cessation of their symptoms upon discontinuation of smoking, and returned to their original status when smoking was resumed. Of the organic group, which included patients with duodenal and gastric ulcers and patients with gastroenterostomy, improvement was noted in refractory cases upon cessation of smoking. Of particular importance was a selected group of 35 patients with duodenal ulcer who were persuaded to cease smoking for one month. Improvement was obtained in only one-third of the patients. However, the period of observation may have been too short, since in our experience refractory patients may respond only after several weeks of abstinence from tobacco. Our results confirm those of Gray, since in patients with peptic ulcer who continue to smoke, regardless of amount, the responsiveness to antacid therapy is very poor. Exacerbations, which may be severe, were also noted in 53 per cent of the patients who smoked. On the other hand, patients who have discontinued smoking or patients who have never smoked, have an excellent prognosis in regard to response to therapy.)

At this point, a summary of the physical and pharmacological properties of tobacco is in order. Tobacco is primarily a vegetable substance which varies tremendously in its constituents, depending upon source, moisture content, aging, processing and many other factors directly concerned with its storage and eventual use. The chemistry of its constituents undergoes alteration by the fact that, in the process of smoking, the composition of the tobacco smoke varies with the manner and rate of smoking. To further complicate the chemistry and ultimate pharmacology of tobacco smoking, the question of inhaling and the probability of greater absorption must be considered. The average moisture content of tobacco is about 12 per cent, with a range from 8 to 50 per cent<sup>18</sup>. The most important ingredient of tobacco and its smoke is nicotine. This varies in different brands of tobacco. The popular blends of cigarettes average 1.5 to 2.5 per cent. The amount of nicotine in tobacco is no criterion of the amount in its smoke. Dixon<sup>19</sup> claims that the water content of the tobacco is much more harmful to the smoker than the original nicotine content of the tobacco because "the drier the tobacco, the

greater the destruction of the nicotine." "During the slow combustion of a cigar, or cigarette, as in ordinary smoking, there is an area immediately behind the point of combustion in which the water and other volatile substances condense. During aspiration, the hot gases are drawn through this hot moist area and carry with them the volatile principles of which nicotine is the most important. Hence the smaller this moist area is behind the point of combustion—which means, the cooler the smoke or the more complete the combustion—the less likely is the smoke to contain volatile toxic bodies."

Asherson<sup>20</sup> stated that 6 to 8 mg. of nicotine reach the mouth from a cigarette smoked in the usual way. This, however, is no indication of the amount absorbed. Lehmann<sup>21</sup> claims that 5 mg. of nicotine is absorbed when the smoke from one cigarette is deeply inhaled. Dixon<sup>19</sup> observed that 3 mg. of nicotine is absorbed when only three-quarters of a cigarette is used and puffed every 12 seconds. He assumes that only 75 per cent of this actually enters the system. The most comprehensive study was by Pierce<sup>12</sup>, who noted that of the nicotine present in burned tobacco about one-third is drawn into the mouth. Of this, the per cent of nicotine inhaled varied between 87.8 to 95 per cent. Pierce also showed that there was very little difference between inhalers and those smokers who merely take the smoke into the mouth. Thus, 2.89 mg. of nicotine was absorbed equivalent to 77.3 per cent of the nicotine present in the smoke. According to these calculations a smoker who inhales deeply will absorb 71.4 mg. of nicotine from one package of 20 cigarettes, while the non-inhalers will absorb 52.8 mg. This is an astonishing amount, since nicotine is one of the most fatal and rapid poisons known. All of this means that tolerance to nicotine is readily acquired in habitual smokers. Direct evidence of tolerance was satisfactorily demonstrated by Johnson<sup>22</sup> who injected  $\frac{1}{10}$  gr. of nicotine into non-smokers with immediate toxic symptoms, while smokers could be given four times this amount without any toxic effect.

✓The literature is practically unanimous in accepting that nicotine is the toxic constituent of tobacco. Although the other ingredients, and even the act of smoking, are contributing factors, the pharmacological as well as the clinical aspects of tobacco smoking are principally due to nicotine.) The pleasure derived from smoking depends upon many factors, such as reflex stimulation from the mucous membranes of the mouth and nose, sight of smoke, aroma, and rhythmical movements of smoking. However, the most important factor is the action of nicotine itself. Johnson<sup>22</sup>, comparing the effects of nicotine injected hypodermically with the effects of smoking, claims that one deep inhalation of cigarette smoke was closely simulated by the intravenous injection of  $\frac{1}{10}$  to  $\frac{1}{20}$  gr. of nicotine. He also noted that the cumulative psychic effect of a cigarette inhaled (approximately 12 inhalations) closely resembled that of  $\frac{1}{10}$  gr. of nicotine by injection. When smokers were given an adequate

dose by injection, they experienced a pleasant effect which satisfied any desire to smoke for some time thereafter.

✓ Brief mention should be made of the other constituents of tobacco and its smoke. In addition to nicotine, tobacco smoke contains ammonia gas, pyridine and other nitrogenous bases, volatile acids, tarry and phenolic substances, furfural and acrolein. It is these ingredients which are responsible for the irritant properties of tobacco smoking, a factor which must be considered as contributing to the pharmacologic effect of smoking. ) They are probably responsible for the irritant effects upon the nasopharynx, upper respiratory tract, conjunctivae, and the reflex stimulation of the salivary secretions<sup>23</sup>. Since they are swallowed in the saliva, they may be a possible factor in the production of some of the symptoms noted in patients. Very few pharmacological studies have been made on the pyridine bases. Dixon<sup>19</sup> mentions their toxic effect such as nausea, vomiting, diarrhea and peripheral collapse. However, he does not think that any significant specific effects could be attributed to these pyridine bases in tobacco smoke and their presence is probably overshadowed by the effects of the nicotine in the smoke. Carbon monoxide and hydrocyanic acid are also present in tobacco smoke but in too low a concentration to be significant.

✓ The final matter for consideration is the mechanism responsible for the unfavorable effects of tobacco smoking upon the clinical course of patients with peptic ulcer. A discussion of the physiological and pharmacological effects of tobacco must take into consideration the effects of (1) tobacco itself, (2) nicotine, (3) other constituents of tobacco, (4) the act of smoking, and (5) the constituents of smoke. The response must be interpreted in the light of the individual tolerance of the smoker, the possibility of reflex alteration of function, the functional capacity of the organ, and its alteration by preexisting disease processes.

It is generally conceded that the effects noted from smoking are due to nicotine. Goodman and Gilman<sup>24</sup> summarize the action of nicotine by stating that "the complex and often unpredictable changes which occur in the body after administration of nicotine are due not only to the several sites of action, but also to the fact that the alkaloid has stimulant and depressant phases of action. The ultimate response of any one structure may thus represent the algebraic summation of the different effects of nicotine." The prime action of nicotine is a direct action upon ganglion cells of both the parasympathetic and sympathetic nervous system, first to excite, then to depress, and finally to paralyze them. Preganglionic impulses are unimpaired, so that the amount of acetylcholine produced at the ganglion is unaltered. Nicotine, however, at first sensitizes the postganglionic fibers to acetylcholine and subsequently inhibits this action. Nicotine also acts directly upon the central nervous sys-



tem, particularly the medullary centers, which are first stimulated and then depressed. The chemoreceptors of the carotid body may also be affected, so that changes may occur reflexly from this center. Finally, nicotine stimulates the production of epinephrine, and many of the observed effects may be due to this factor. To further complicate the picture, reflex changes may occur secondary (1) to irritation of the mucous membranes of the upper respiratory passages and pharynx by the hot smoke or by the ingredients of the smoke and (2) to deep breathing. There is no wonder, therefore, that marked confusion exists regarding the importance of nicotine as an etiologic factor in gastrointestinal disorders. Since so many effects may be noted, depending upon the method of study and type of control, it is not unusual for investigators to reach exactly opposite conclusions. This is in itself the best argument in favor of nicotine as the responsible factor since variant results are definitely linked to the diverse pharmacological effects that could occur.

In this report we are not at present concerned with the manner by which tobacco smoking affects the physiological function of the stomach. Clinically, considering the patient as a whole, it can be concluded that tobacco smoking is detrimental to the welfare of a peptic ulcer patient. Not only will response to antacid therapy be inadequate but the likelihood of severe exacerbations is approximately three to four times that of non-smokers or patients who have ceased smoking. If the patient cannot give up smoking completely, the use of partially denicotinized tobacco is the best compromise. It is possible by the use of such tobacco in a group of refractory patients to increase the responsiveness to antacids and decrease the incidence of exacerbations, but the results do not approximate those in patients who are persuaded to stop smoking entirely.

#### SUMMARY AND CONCLUSIONS

1. The influence of smoking on the management of the peptic ulcer patient was evaluated in 108 patients.

2. Patients who continued to smoke had a poor response to treatment, so that the effectiveness of antacid therapy was no greater than 47 per cent. The inadequacy of treatment was reflected in the high incidence (53 per cent) of acute exacerbations.

3. Patients who discontinued smoking or never smoked had an excellent response to antacid therapy, so that the incidence of acute exacerbation decreased to 11.5 and 17.5 per cent respectively.

4. In a group of 28 patients refractory to an ambulatory regime of antacid therapy when smoking regular tobacco, the use of a processed or partially denicotinized cigarette resulted in improvement of 22 of the patients, with the incidence of acute exacerbations decreasing from 53.5 per cent to 29 per cent.

5. Reinstitution of smoking tobacco of full nicotine content, in 18 patients, who had shown improvement with the partially denicotinized tobacco, resulted in decreased effectiveness of antacid therapy and an increase in the incidence of exacerbations to a level corresponding to the control level.

6. The pharmacology of nicotine and the status of smoking in the production of peptic ulcer are discussed.

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## THE EFFECT OF INTRAVENOUS PROTEIN HYDROLYSATES ON THE STOMACH

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### INTRODUCTION

Protein and products of protein digestion are known to be gastric secretagogues. Pavlov and Chigin<sup>1</sup> showed that oral administration of meat extractives, proteoses and peptones stimulates the stomach to secrete a large volume of highly acid juice. Okada et al<sup>2</sup> reported that the amino acids glycocoll (glycine) and d-alanine stimulated gastric secretion of free acid when administered intravenously, and that this effect was inhibited by atropine, vagotomy, or by mixing the amino acid with a dextrose solution prior to administration. The intravenous injection of meat extractives and products of peptic hydrolysis causes a relatively small gastric secretory response.<sup>3</sup> Ivy and Javois<sup>4</sup> reported that protein hydrolysates given by stomach tube stimulated gastric secretion by acting on the intestine and that this response was abolished by one mg. of atropine subcutaneously. They further noted that subcutaneous injection of hydrolysates of meat or casein, or of individual amino acids, did not increase gastric secretion.

Ever since Elman and Weiner<sup>5</sup> showed that it was possible to correct hypoproteinemia by the intravenous administration of amino acid mixtures (acid hydrolysate of casein with 2 per cent tryptophan and cystine added), protein hydrolysates have been extensively used in the management of many diseases. Because at the present time wide use is made of protein hydrolysates, particularly in the pre- and postoperative management of patients undergoing gastric surgery, and because previous reports<sup>2, 3</sup> have indicated that amino acids given intravenously stimulate gastric acid formation, we deemed it important to study further the effect of intravenously given protein hydrolysates on gastric acidity and motility.

### MATERIAL AND METHOD

One-hundred-and-sixty-two gastric analyses were performed: 153 during the intravenous infusion of protein hydrolysates, 5 during infusion of plasma, and 4 during infusion of 10 per cent dextrose. One-hundred-and-six of these analyses were performed on patients who had no gastric complaints; 50 tests were made of peptic ulcer patients, and 6 on a patient with hypertrophic gas-

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tritis. Motility studies were made in 5 patients free of gastrointestinal disease. Nine of the 106 tests revealed an achlorhydria to 0.6 mg. or 1 mg. of histamine phosphate given subcutaneously. A small group, consisting of approximately 6 peptic ulcer patients and 5 patients with normal stomachs, was tested repeatedly by the use of a different protein hydrolysate each day. All of these patients were tested with the substances shown in Table II.

Each test was conducted in the morning, after a 16 hour fast. The stomach was emptied with the aid of a Levine tube, and the amount and acidity of the gastric residuum was noted. An intravenous infusion of physiological saline, or 2.5 per cent glucose in 0.4 per cent saline solution, was then started and the flow was adjusted to a rate of approximately 72 drops per minute. A control period of secretion was obtained for 45–50 minutes prior to the intravenous administration of the test material. The stomach contents were aspirated continuously. Fifteen minute samples were measured for volume and titrated with 0.1 N NaOH for free and total acid, using Topfer's reagent and phenolphthalein as the indicators. For the motility studies, the same tests were made and, in addition, a balloon was passed into the fundus of the stomach. A small amount of air (10–15 cc.) was placed in the balloon, the tube was attached to a water manometer, and recordings were made on a slowly moving kymograph.

Five patients were tested with a protein hydrolysate before and after vagotomy. In all 5 the insulin test, as conducted by Stein and Meyer,<sup>6</sup> indicated a complete vagus section. The routine tests, previously described, were performed on the fourth postoperative day. Three patients were tested after bilateral thoracic sympathectomy and splanchnicectomy for hypertension.

The effect of atropinization on the gastric acidity stimulated by the intravenous administration of protein hydrolysates was tested in 9 patients. In 3 instances  $\frac{1}{16}$  grain atropine sulfate was given intravenously, in 3 others  $\frac{1}{80}$  grain and in 3 patients  $\frac{1}{16}$  grain. The atropine was injected 75 minutes after the start of the protein hydrolysate infusion. The latter was continued for another hour and the gastric acidity determined as described above.

The following protein hydrolysate solutions were used:

A. 6 per cent acid hydrolysate of casein in distilled water with added tryptophane, methionine, and glycine. This product was in storage for about one year prior to use.

B. Same as A but recently prepared.

C. 5 per cent enzymatic (pancreatic) hydrolysate of casein in 5 per cent dextrose solution.

D. 6 per cent lyophilized acid hydrolysate of casein with added tryptophane, in distilled water.

E. Same as D except for a reduced amount of glutamic and aspartic acids.

E<sub>1</sub>. Same as E except that the diluent was 5 per cent dextrose solution.

F. 5 per cent partial acid hydrolysate of blood fibrin, in 5 per cent glucose solution.

G. 5 per cent enzymatic hydrolysate of bovine plasma in distilled water.

TABLE I  
*The effect of protein hydrolysates on gastric acidity*

PROTEIN HYDROLYSATE			NO. OF TESTS		POSITIVE TESTS			
Product	Histamine content*	pH	Total	No. with increased acid	Aver. of highest 15 min. control period		Aver. of highest 15 min. test period	
					Free acid, clinical units	Vol.	Free acid, clinical units	Vol.
	<i>μgm./cc.</i>					<i>cc.</i>		<i>cc.</i>
A.....	0.22	4	19	18 (95%)	29	19	66	35
B.....	0.09-0.1	4	24	17 (70%)	24	21	65	21
C.....	0.03-0.05	6.5	19	5 (26%)	27	19	62	26
D.....	Less than 0.02	6.5-7	11	2 (18%)	15	12	61	28
E.....	Less than 0.02	6.5-7	14	7 (50%)	18	18	61	36
F.....	0.15	5.2-5.5	19	9 (47%)	31	20	58	26
Average.....			106	58 (55%)	24	18	63	29

\* Histamine assay on atropinized cat's blood pressure. Vasodepression abolished by an antihistaminic.

TABLE II  
*The effect of various protein hydrolysates on gastric acidity in the same patients*

PRODUCT	HISTAMINE ASSAY* OF HYDROLYSATE	pH OF HYDROLYSATE	NON-ULCER PATIENTS		ULCER PATIENTS	
			No. of tests	Increased acidity %	No. of tests	Increased acidity %
	<i>μgm./cc.</i>					
B.....	0.09-0.1	4	5	3 (60%)	6	4 (66%)
C.....	0.03-0.05	6.5	4	1 (25%)	6	2 (33%)
E.....	Less than 0.02	6.5-7	5	2 (40%)	5	3 (60%)
E <sub>1</sub> .....	Less than 0.02	6.5-7	4	1 (25%)	3	1 (33%)
F.....	0.15	5.2-5.5	5	2 (40%)	6	4 (66%)
G.....	0.02-0.03	6.2	5	2 (40%)	2	1 (50%)
G <sub>1</sub> .....	0.05	5.7	4	0	5	0

\* Histamine assay on atropinized cat's blood pressure. Vasodepression abolished by an antihistaminic.

G<sub>1</sub>. Same as G except that the diluent used was 5 per cent dextrose solution.

## RESULTS

In the 106 tests performed after injection of various protein hydrolysates, increased gastric acidity was obtained in 55 per cent of instances (Table I).

All test solutions stimulated gastric secretion in some cases. Product A gave an increased acidity in 95 per cent of the tests performed, B in 70 per cent, E in 50 per cent, F in 47 per cent, C in 26 per cent and D in 18 per cent (Table I).

In the group which was tested with different protein hydrolysates daily (Table II), the percentage found to have increased gastric acid response to the individual test substances was somewhat similar to the percentage having increased gastric acid response (Table I) in the group receiving only one preparation.

TABLE III

*Effect of vagotomy on gastric response to protein hydrolysates*

	NO. OF PATIENTS	NO. OF PATIENTS SHOWING INCREASED ACID	HIGHEST AVERAGE ACID LEVEL IN 15 MIN. PERIOD
Before vagotomy.....	5	5	90 clinical units
After vagotomy.....	5	5	71 clinical units

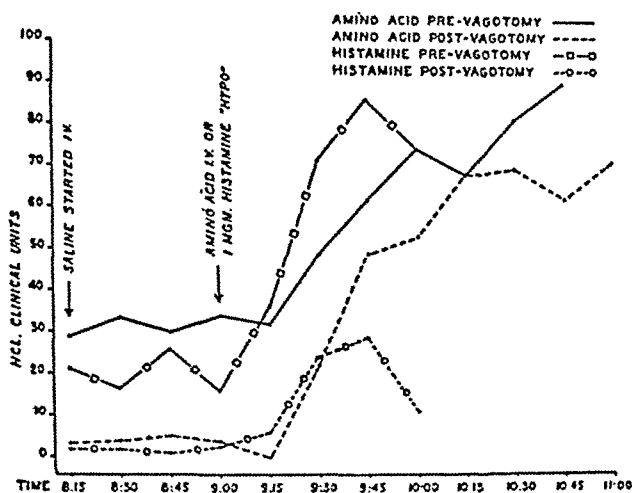


FIG. 1. THE EFFECT OF INTRAVENOUS PROTEIN HYDROLYSATES AND HISTAMINE IN THE SAME PATIENTS BEFORE AND AFTER VAGOTOMY

The 5 patients with complete vagotomy showed an increase in gastric acidity during the intravenous administration of 6 per cent protein hydrolysate in distilled water (A & B), both before and after vagotomy. The highest average response in one 15 minute period was 90 clinical units of free acid before, and 71 clinical units after vagotomy (Table III, Fig. 1).

Three patients tested after a bilateral thoracic sympathectomy and splanchnicectomy showed an increased gastric acidity during the test period.

The 5 patients given plasma infusions showed no stimulation of gastric acidity. Four patients who received an infusion of 10 per cent dextrose solution showed an actual decrease in gastric acidity (Fig. 2, Table IV).

In the 5 patients given an infusion of protein hydrolysates, gastric motility

remained unchanged during the administration. In 3, the acid response was increased; in the remaining 2 no acid studies were made.

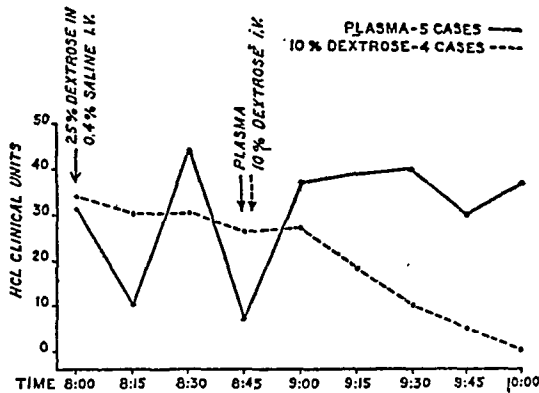


FIG. 2. THE EFFECT OF PLASMA AND 10% DEXTROSE ON GASTRIC ACIDITY

TABLE IV

*The effect of plasma and 10 per cent dextrose on gastric acidity*

NO. OF CASES	PRODUCT	CONTROL PERIOD		TEST PERIOD	
		Aver. high acid/15 min.	Aver. high vol./15 min.	Aver. high acid/15 min.	Aver. high vol./15 min.
		units	cc.	units	cc.
5	Plasma (dried)	18	22	19	19
4	10% dextrose in water	39	43	20	23

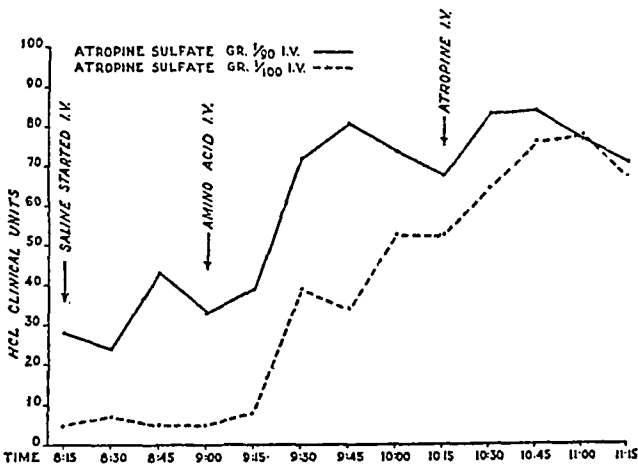


FIG. 3. THE EFFECT OF ATROPINE SULFATE ON GASTRIC ACIDITY STIMULATED BY PROTEIN HYDROLYSATES

In the 3 patients given  $\frac{1}{50}$  grain of atropine intravenously the gastric acidity continued to rise in 2 instances and fluctuated at high levels in the other patient. The gastric acidity continued to rise in each of the three patients given  $\frac{1}{100}$  grain atropine intravenously during the protein hydrolysate infusion (Fig.

3). In the 3 patients given 1/60 grain atropine the gastric acidity definitely decreased.

### DISCUSSION

An increase in gastric acidity following intravenous administration of amino acids and protein hydrolysates was first reported by Okada<sup>2</sup> and others.<sup>3</sup> In our series of cases studied, similar observations were made. The acid response seemed to be partially conditioned by various factors. One factor was the presence or absence of glucose. Thus protein hydrolysates in dextrose solution gave an acid increase in only 35 per cent as compared to 64 per cent following the infusion of protein hydrolysates in distilled water (Table V). The

TABLE V

*Relationship of diluent of protein hydrolysate to gastric acid production*

DILUENT	NO. OF TESTS	NUMBER WITH INCREASED GASTRIC ACID
Distilled water.....	68	44 (64%)
5% dextrose.....	37	13 (35%)

TABLE VI

*Comparison of effect of diluent of protein hydrolysates on gastric acidity in patients tested with the same preparation*

MIXTURE	NO. OF TESTS	NUMBER WITH INCREASED ACID
E—in distilled water.....	10	5 (50%)
E <sub>1</sub> —in 5% glucose.....	7	2 (28%)
G—in distilled water.....	7	3 (43%)
G <sub>1</sub> —in 5% dextrose.....	9	0

same protein hydrolysate dissolved in dextrose solution and in distilled water gave different acidity responses in the same patient, (i.e., 47 per cent with distilled water and 12 per cent with 5 per cent dextrose solution) (Table VI). These results are similar to those of Okada,<sup>2</sup> who also noted an inhibition of gastric acidity when the amino acids were administered with dextrose. Moreover, the intravenous administration of 10 per cent dextrose to 4 patients failed to provide an acid increase; instead, it markedly decreased the gastric acidity (Fig. 2, Table IV). This finding has also been reported by others.<sup>7, 8, 9</sup>

The pH of the infused solution was another factor which seemed to influence somewhat the gastric acid response. Thus, the protein hydrolysates with a pH 4 gave an increased acid response in 81 per cent of 43 tests, as compared to 31 per cent of 44 tests with solutions having a less acid pH, 6.5–7.0 (Table VII).

The main factor governing the response of gastric acidity to infusion of pro-



tein hydrolysates seems to be the histamine content of these solutions. The presence of histamine-like substances in protein hydrolysates was observed by Hopps and Campbell.<sup>10</sup> Hanson, Grossman and Ivy<sup>11</sup> have shown that the intravenous threshold dose of histamine needed to produce an acid response in the human stomach is 0.004 micrograms/Kg. per minute. Infusion at this rate will not cause a detectable rise in blood histamine. The histamine content of those products tested on the same patient\* varied from less than 0.02 to 0.15 micrograms/cc. The preparations (B and F) containing 0.09-0.1 micrograms/cc. and 0.15 micrograms/cc. respectively, stimulated acid production in 60 per cent of the tests performed; the other preparations, having a

TABLE VII

*Relationship of pH of protein hydrolysates to gastric acid production*

NO. OF TESTS	NUMBER WITH INCREASE IN GASTRIC ACIDITY	pH
43	35 (81%)	4
44	14 (31%)	6.5-7

TABLE VIII

*Relationship of histamine content of protein hydrolysates to gastric acidity in the same patients*

PRODUCT	NO. OF TESTS	NUMBER WITH INCREASED ACIDITY	HISTAMINE  μmg./cc.
B.....	11	7 (63%)	0.09-0.1
C.....	10	3 (30%)	0.03-0.05
E.....	17	7 (41%)	Below 0.02
F.....	11	6 (54%)	0.15
G.....	7	3 (43%)	0.02-0.03
G <sub>1</sub> .....	9	0	0.05

histamine content between less than 0.02 and 0.05 micrograms/cc. stimulated acid production in 30 per cent of the tests performed (Table VIII).

The preparations with the least amount of histamine (C, D, E and G) did not provide the minimal amount of histamine necessary to produce an increase in gastric acidity.<sup>11</sup> Yet these preparations stimulated gastric acid production, as mentioned previously (Table I and II). Though the histamine content of the protein hydrolysate undoubtedly is an important factor in the production of gastric acidity, we, nevertheless believe that there are other factors present; these may stimulate acid production and may act in the presence or absence of histamine.

The preparation containing the second highest amount of histamine, F

\*Histamine assay on atropinized cat's blood pressure; vasodepression abolished by an anti-histaminic. Performed by Dr. R. Richards, Abbott Labs.

(0.15 micrograms/cc.), gave a smaller number of positive reactions than the preparation with the next highest quantity of histamine, B (0.09-0.1). The discrepancy can be explained by the diluent used. Preparation F was dissolved in 5 per cent glucose, whereas B was dissolved in distilled water. This explanation could be supported by the work of Day and Komarov,<sup>8</sup> who have shown that the intravenous administration of dextrose solution inhibits the gastric secretory response to an injection of histamine.

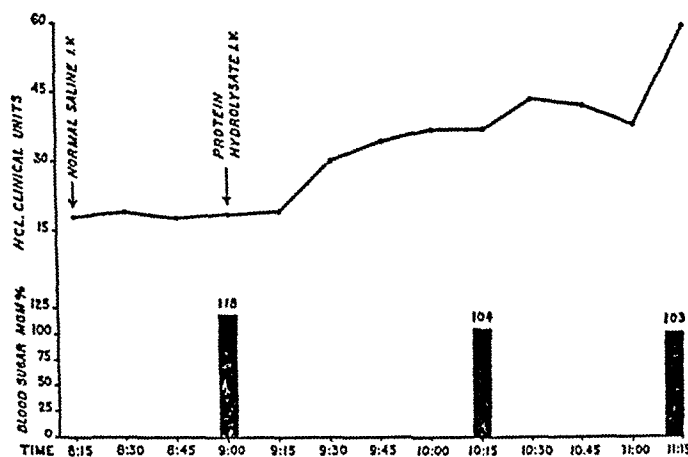


FIG. 4. RELATIONSHIP OF BLOOD SUGAR TO GASTRIC ACIDITY STIMULATED BY INTRAVENOUS PROTEIN HYDROLYSATES

TABLE IX

*Effect of intravenous protein hydrolysate on blood sugar*

NUMBER OF PATIENTS STUDIED	PRODUCTS	BLOOD SUGAR			INCREASE IN GASTRIC ACIDITY	NO GASTRIC ACIDITY INCREASE
		Decreased	Unchanged	Increased		
29	Varied protein hydrolysates	16*	9	4	22	7

\* Hypoglycemic level (58 mgm. %) in one instance; when repeated a normal response of 100 mgm. % was obtained.

Another possible factor, as suggested by Okada<sup>2</sup> is the occurrence of hypoglycemia during the intravenous infusion of amino acids, which in turn leads to an increased acid secretion. Blood sugar studied in 28 patients did not support the above hypothesis for the changes in blood sugar were not found to be significant (Fig. 4, Table IX).

The fact that the oldest solution, A (stored for one year prior to using) contained the most histamine (0.22 micrograms per cc.) suggested the possibility that histamine was liberated in this solution on standing. However, this possibility was not confirmed by a repeat histamine analysis\* 4 months later

\* Performed by Doctor Karl Urbach, Department of Pharmacology, Northwestern University Medical School.

which revealed the same amount of histamine (0.22 micrograms per cc.) as in the first analysis.

If histamine should prove to be the factor responsible for the increased acidity, then intravenous administration of solutions in which histamine is present may be harmful, particularly in patients who have recently undergone gastric surgery. Price and Lee,<sup>12</sup> and Dragstedt,<sup>13</sup> have reported that highly acid gastric juice will digest living tissue in a short time. The former<sup>12</sup> have shown in dogs that the injection of histamine in beeswax, would cause spontaneous ulceration in the previously healthy stomach and duodenum. They also noted that jejunal implants in the wall of the stomach were digested sufficiently in one day to cause perforation when histamine in beeswax was given.

Since dextrose solutions of protein hydrolysates are less likely to produce increased gastric acidity than aqueous solutions, it follows that the former should be preferred for parenteral use. The dextrose solution not only decreases the amount of acid secreted but it also adds caloric value; furthermore, as some investigators have reported,<sup>5</sup> it enhances the utilization of the infused amino acids. Finally, it appears that in the presence of hyperglycemia, gastric acid response to histamine is reduced.<sup>8</sup>

Our inability to find changes in gastric motility during the intravenous infusions of protein hydrolysates is in agreement with the work of Bowman;<sup>14</sup> he showed in dogs that the intravenous infusion of individual amino acids and of mixtures of amino acids as found in casein digests, failed to change the length, frequency or amplitude of periods of gastric motility.

We have been unable to confirm Okada's observation<sup>2</sup> that vagotomy inhibited the gastric secretion of free acid in response to the intravenous administration of amino acids.

Similarly we found that  $\frac{1}{16}$  or  $\frac{1}{32}$  grain of atropine sulfate given intravenously during the protein hydrolysate infusion failed to decrease the gastric acid response to the infusion. Thus, in 5 of 6 instances there was a slight rise in gastric acidity following these doses of atropine while in one the acidity fluctuated at a high level. In three patients, however,  $\frac{1}{16}$  grain atropine given intravenously produced a definite decrease in gastric acidity during the infusion of protein hydrolysate. At present the significance of these findings is conjectural. Parenteral administration of protein hydrolysate in 3 patients after thoracic sympathectomy and splanchnicectomy produced stimulation of gastric secretion.

The above findings suggest that stimulation of the stomach by intravenously administered protein hydrolysates may be due to one factor alone, or to a combination of factors. These factors may be (a) the histamine content, (b) the pH of the solution, (c) direct stimulation of the gastric glands by the protein

hydrolysate itself or by a hormone liberated by it, and (d) any combination of the foregoing.

#### SUMMARY

1. Protein hydrolysates, administered intravenously, stimulated gastric acidity in 55 per cent of tests performed.

2. Factors influencing the acidity were (a) histamine content, (b) pH of the solution, (c) the nature of the diluent used with the protein hydrolyaste.

3. Protein hydrolysates in 5 per cent dextrose solution produced gastric stimulation in less instances than those in distilled water.

4. Gastric motility was unaffected by intravenous administration of protein hydrolysates.

5. Neither vagotomy nor thoracic sympathectomy and splanchnicectomy inhibited the gastric response to parenteral protein hydrolysates. Atropine sulfate in small doses given intravenously did not reduce the gastric acidity stimulated by protein hydrolysate infusion; a larger dose,  $\frac{1}{8}$  grain, noticeably decreased the acid response.

6. Stimulation of gastric acid formation by intravenously administered protein hydrolysates is probably accomplished through (a) a relatively high histamine content, (b) an acid pH, (c) direct action on the gastric glands by the hydrolysate itself, or by a liberated hormone, or (d) by a combination of the three foregoing factors.

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## LETHALITY RATE OF HEMATEMESIS AND MELENA TREATED NON-OPERATIVELY (MEULENGRACHT'S REGIMEN) AND CRITERIA FOR SURGICAL INTERVENTION IN BLEEDING PEPTIC ULCER\*

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### INTRODUCTION

The treatment of bleeding peptic ulcer has mainly been non-operative, during the last 10 years in most hospitals consisting of rather liberal feedings and blood transfusions. The lethality is lower than earlier when food and fluids were withheld, and at the present time it must be considered low, calculated on the basis of *all* cases of hematemesis and melena from peptic ulcer.

However, deaths still occur from hemorrhage during this treatment. Judging from the post-mortem findings the fatal hemorrhage might in some cases have been arrested by surgical measures, but on the whole surgical intervention is comparatively seldom used. Formerly a not-inconsiderable lethality in surgery on the stomach gave rise to a certain reservation in advising operation. During recent years this operative lethality has fallen so much that surgical intervention might be considered for some cases of bleeding peptic ulcer. The difficulty is then concerned with selecting the right cases for operation. This is no easy matter, as the hemorrhages involving death from exsanguination only constitute a small part of the numerous hemorrhages which are arrested spontaneously or by the non-operative treatment. The main reason for the conservative measures commonly adopted may perhaps be stated as "the absence of any really trustworthy guide to prognosis at an early stage after which the information becomes less and less valuable—" (Eusterman<sup>1</sup> citing an editorial in *British Medical Journal*).

It would then appear to be a question of whether it is possible to separate a well-defined, suitably large group of hemorrhages in which the lethality by conservative treatment is so high that surgical intervention must be considered and whether simple and easily recognizable diagnostic criteria can be established for this group at an early stage of the hemorrhage.

This paper is an attempt at establishing such a group, and at discussing the appropriateness of surgery in these cases. For this end an analysis has been made of the lethality rate in a large material of bleeding peptic ulcer cases, treated by the non-operative method of prompt, free and frequent feeding and blood transfusions (Meulengracht<sup>2</sup>). The analysis forms a continuation of earlier studies of hematemesis and melena<sup>3, 4</sup>, which are briefly reviewed below.

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## OPERATIVE CRITERIA SET UP EARLIER

Opinions have been extremely divided among surgeons as to the indication for operation upon acute cases of bleeding peptic ulcer, ranging from operation in all chronic ulcers within 48 hours of the onset of hemorrhage (Finsterer<sup>6</sup>) to the utmost conservatism. During recent years, however, even the active surgeons appear to be agreed that non-operative treatment should be the rule. Those surgeons who operate upon an acute bleeding peptic ulcer, only do so in a small number of the cases, and several workers have proposed criteria to single out the surgical cases. The literature will not be dealt with in detail. Allen<sup>6</sup>, Wangenstein<sup>7</sup>, Heuer<sup>8</sup>, Gordon-Taylor<sup>9</sup> and Bohmansson<sup>10</sup> int. al. comment on the American, British and Scandinavian literature respectively.

The criteria established by the various authors are somewhat varied, but they have certain main features in common. The patients must be at least 40-50 years of age, an ulcer niche must have been demonstrated, the hemorrhage must be profuse, repeated, persistent in spite of appropriate treatment or have arisen during treatment. These criteria are of great prognostic value. However, the last item regarding the hemorrhage does not only mean that the patients are given individual treatment, according to good clinical practice, but also that a long time may elapse before the criterion is fulfilled. One must wait and it may be difficult to find out whether the hemorrhage is repeated or persists. Thereby one may miss the most favorable moment for surgical intervention, and at times the patient may die before the operation is performed. We lack a criterion which predicts the prognosis with some certainty at an early stage of the hemorrhage.

## WRITER'S INVESTIGATIONS

*Previous Investigations*

Studying a post-mortem material from some medical departments in Copenhagen the writer found 145 cases of bleeding peptic ulcer of which 121 (85 per cent) had exhibited hematemesis and 24 (15 per cent) melena. The great predominance of hematemesis among the deaths gave rise to a more detailed study of the difference between hematemesis and melena<sup>3, 4</sup>. The conclusion of these investigations was that hematemesis is a much more serious form of hemorrhage than melena. This is primarily due to the fact that hematemesis is considered a more *rapid* hemorrhage than melena, not to the loss of blood necessarily being greater in hematemesis than melena. When the loss of blood has exceeded a certain amount, the risk of the hemorrhage depends more on its *rapidity* than its amount. A large red hematemesis is both a large and a rapid bleeding. The mode of manifestation depends on the size and nature of the blood vessels and the nature of the ulcers in the various regions of the stom-

ach and duodenum. In 85 per cent of the fatal cases there was an eroded blood vessel, and a large, red hematemesis from peptic ulcer practically always means erosion of an artery. In 90 per cent the lesion was a real peptic ulcer, in 10 per cent an erosion or gastritis. During the decade 1937-46 94 per cent of 107 fatal cases were 40 or more years, 82 per cent 50 or more years of age.

These findings have been applied to the clinical material submitted in this paper and form the basis of the analysis.

### *Present Investigations*

The original material comprises all cases of peptic ulcer and ulcer disease exhibiting hematemesis or directly visible melena, a total of about 850\*, admitted to the Medical Department B of the Bispebjerg Hospital, Copenhagen during the decade from May 1, 1938 to April 30, 1948.

### *Treatment*

The treatment was the said non-operative method used by Meulengracht<sup>2</sup> since 1931. Only 1 patient was submitted to operation. In the course of time blood transfusion has come to occupy a more and more important position. Of the analysed material mentioned below 15 per cent of the patients received blood transfusion during the first 8 years, but 32 per cent during the last 2 years of the decade in question.

### *The Dead*

All deaths from and with manifest hemorrhage from peptic ulcer are included and great energy has been used to trace them all. All post-mortem records (about 2,500) during the decade in question have been perused, int. al. to include those in which the bleeding has not had time to manifest itself *in vivo* and those in which the primary clinical diagnosis was not correct. The material also includes the death following the one operation (Table 1 A, No. 12). There is a rather large contingent in which the hemorrhage was not the main cause of death and a few who died after having recovered from the loss of blood.

Table 1 sets out all 31 dead, divided into 2 main groups, A and B.

A. 17 cases. Death is exclusively or mainly due to exsanguination. In cases exhibiting complications the latter are not too severe to bar an attempt at saving the patient. The possibility of subjecting the patients to surgery with some success has been estimated. Fifteen exhibited an eroded blood vessel, 12 received transfusions. Average age: about 60.

\* The exact number was not counted as it is of minor consequence in this study. (See Table 2.)

In Copenhagen practically all cases of hematemesis and melena are hospitalized, int. al. because it is very cheap to stay in hospital. 86 per cent of the population are members of sickness benefit societies and need not pay anything for the stay in hospital, except the subscription to the society, no matter how long their stay or how expensive the examinations and treatment. As a matter of routine patients with hematemesis and melena are admitted to the medical departments.



TABLE 1  
*Deaths*

A. Cause of death: Exsanguination

CASE NUMBER	MANIFESTATION OF HEMORRHAGE	SEX	AGE	TIME OF BLEEDING AFTER ADMISSION	INTERVAL BETWEEN ADMISSION AND DEATH	CLINICAL NOTES AND POST MORTEM FINDINGS	SURGERY
1	Melena	♂	65	First and third day	3 days	Transferred from a surgical department. Angina pectoris for some years. 37 days before transfer transurethral resection for enlargement of the prostate. 36 days before transfer gross bleeding per urethram. Explorative laparotomy showed gross bleeding from the bladder. 1000 ml. blood transfused. 14 days before transfer hematuria ceased. 1 day before transfer melena several times. He grew irrational and suffered from severe attacks of angina pectoris. 500 ml. blood transfused; exsanguinated and irrational when transferred. On admission 500 ml. blood transfused, later on transfusions impossible. His peptic ulcer was unknown. Autopsy: Severe arteriosclerosis. Hypertrophy of the prostate. Adenomatous polypus in the bladder. Large chronic gastric ulcer, 5.5 by 3 cm., on the lesser curv. Multiple blood vessels eroded.	Possible ? (high resection of the stomach)
2	Hematemesis before admission	♀	59	(Melena) (<1 day)	<1 day	Lean. Severe chronic polyarthritis. Clinical diagnosis: Cancer of the stomach ? Autopsy: Erosive gastritis of prepyloric region, 4 by 6 cm. Multiple blood vessels eroded.	Possible ? (X-ray perhaps negative)
3	Hematemesis in hospital	♂	26	Second and seventh day	9 days	Syringomyelia. Autopsy: Chronic duodenal ulcer, 2 by 3 cm. Blood vessel eroded.	Possible
4	Hematemesis in hospital	♂	46	First and second day	2 days	Severe chronic polyarthritis. Clinical diagnosis: Cancer of the stomach ? Autopsy: chronic prepyloric ulcer on the posterior wall, 4 by 4 cm. penetrating to the omentum. No adhesions to other organs. Large eroded blood vessel.	Possible

5. TONER OF WR 4 BY 4 cm. Penetrating to the  
 stomach. No adhesions to other organs. Large  
 eroded blood vessel.

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5	Hematemesis in hospital	♂	53	Fourth day	9 days	Heart disease. Autopsy: two small chronic duodenal ulcers, large eroded blood vessel. Cardiac hypertrophy and arteriosclerosis.	Possible
6	Hematemesis in hospital	♂	57	First day	2 days	Autopsy: chronic duodenal ulcer, 1 by 1 cm., eroded blood vessel.	Possible
7	Hematemesis in hospital	♂	58	Thirteenth and sixteenth day	17 days	Cachexia, pyloric stenosis. Clinical diagnosis: Cancer of duodenal ulcer, 3 by 3 cm. penetrating to the pancreas, gastroduodenal artery eroded.	Possible
8	Hematemesis in hospital	♂	67	First day	7 days	Chronic bronchitis and emphysema, hypertrophy of the prostate. Autopsy: Gastroenterostomy and jejunal hypertrophy.	Possible
9	Hematemesis in hospital	♂	70	First day	25 days	Transferred from a surgical department. Hypertrophy of the prostate and adiposity. Autopsy: chronic duodenal ulcer, 3 by 3 cm., penetrating to the pancreas, the hepatic (?) artery eroded. Cardiac hypertrophy and enlargement of the prostate.	Possible
10	Hematemesis in hospital	♂	76	First and second days	2 days	No distinct arteriosclerosis. Autopsy: chronic duodenal ulcer, 2 by 2 cm. Gastroduodenal artery eroded.	Possible
11	Hematemesis in hospital	♀	51	First day	2 days	Autopsy: Chronic duodenal ulcer, large eroded blood vessel. Right-sided purulent sacculpinx with com- pression of the ureter and slight hydronephrosis.	Possible
12	Hematemesis in hospital	♀	51	Seventh to thirteenth day (in the medical depart- ment)	23 days	Slight adiposity. Surgical intervention on nineteenth day after repeated transfusions, on vital indication. Resection and excision impossible. Duodenotomy and transfixion of bleeding blood vessel was performed. Died of hematemesis on the fourth day after the opera- tion. Autopsy: chronic duodenal ulcer, 1 by 1 cm., a large blood vessel eroded (transfixed).	Possible (see clinical notes)

TABLE 1—Continued

CASE NUMBER	MANIFESTATION OF HEMORRHAGE	SEX	AGE	TIME OF BLEEDING AFTER ADMISSION	INTERVAL BETWEEN ADMISSION AND DEATH	CLINICAL NOTES AND POST MORTEM FINDINGS	SURGERY
13	Hematemesis in hospital	♂	47	First to third day	3 days	Cachexia, renal disease. Autopsy: Gastroenterostomy. Gastrojejunal ulcer penetrating to the abdominal wall. Cardiac fibrosis and hypertrophy, renal sclerosis.	Impossible
14	Hematemesis in hospital	♂	58	Tenth day	12 days	Aortic aneurysm for some years. Autopsy: chronic duodenal ulcer, 4 by 5 cm., penetrating to the liver, large eroded blood vessel. Syphilitic aortitis and large aortic aneurysm, renal sclerosis.	Impossible
15	Hematemesis in hospital	♀	69	First day	<1 day	Hypertensive heart disease, nephritis. Autopsy: chronic prepyloric gastric ulcer, 1 by 1 cm.; eroded blood vessel. Cardiac hypertrophy, syphilitic aortitis, arteriosclerosis, nephrosclerosis.	Impossible
16	Hematemesis in hospital	♀	68	First day	3 days	Cachexia, severe heart disease. Autopsy: chronic gastric ulcer of the lesser curvature, 5 by 7 cm., with a cavity as large as a hen's egg, penetrating to the liver and pancreas; large eroded blood vessel. Large left-sided pleuropneumonia, severe cardiac fibrosis and arteriosclerosis.	Impossible
17	Hematemesis in hospital	♀	82	First and second day	2 days	Irrational. Clinical diagnosis: Cancer of the stomach ?. Autopsy: two chronic duodenal ulcers, 1 by 1 cm., penetrating to the omentum, cardiac fibrosis and arteriosclerosis, no visible blood vessels.	Impossible
B. Cause of death: Varied. Operation impossible or counter-indicated							
					CLINICAL NOTES AND POST MORTEM FINDINGS		
18	None	♂	65	Unknown	3 days	High-febrile, irrational on admission. Internal bleeding not diagnosed. Autopsy: Purulent meningitis. Severe cardiac and vascular arteriosclerosis. Stomach and intest. canal filled with blood. Chronic ulcer, 1 by 1 cm., in the pylorus, two 1 by 1 cm. fresh ulcers nearby.	

Autopsy: Purulent meningitis. Severe cardiac and vascular arteriosclerosis. Purulent stomach and intestinal canal filled with blood. Chronic ulcer, 1 by 1 cm., in the pylorus. Last 1 by 1 cm. fresh ulcer, reactive. Chronic ulcer.

19	None	♂	76	Unknown	1 day	Severe cardiac failure with perp. arrhythmia. Internal bleeding not diagnosed. Clinical suggestion: Cancer of the stomach. Autopsy: cardiac fibrosis and arteriosclerosis. Purulent bronchitis and pneumonia. Melena in the intestinal canal. Chronic prepyloric ulcer, 1 by 1 cm.
20	Melena	♂	62	10 minutes	10 minutes	Severe heart disease for years and mental disease, frequent admissions to mental hospitals. Autopsy: cardiac hypertrophy and severe arterio- loric ulcer of the stomach, 1 by 1 cm., perforating to the omentum; large eroded blood vessel.
21	Melena	♂	63	First day	2 days	Transferred from a surgical department. Known cancer with metastases to Cachexia. Autopsy: Cancer of the left lung, with metastases to different viscera. Simple (microsc.) chronic ulcer, 4 by 6 cm., of the stomach, penetrating to the liver.
22	Hematemesis before admission	♂	70	(Melena second day)	18 days	Heart disease and hypertrophy of the prostate. The last two weeks before death no benzidine reaction in feces. Lowest hb, per cent. 66. Autopsy: Hypertrophy of the prostate with bilat. hydronephrosis. Old cardiac infarct. ulcer, 1 by 1 cm., adherent to the pancreas. Eroded blood vessel.
23	Hematemesis before admission	♂	73	(Melena first and second day)	27 days	Adiposity and chronic nephritis, thrombophlebitis of lower extremity. The day of death hb. 78 per cent. Autopsy: Embolus of pulm. artery. Renal sclerosis, hypertrophy of the prostate. Chronic duodenal ulcer, 2 by 2 cm.
24	Hematemesis before admission	♂	75	(Melena <2 hours)	2 hours	Hemiparesis. Clinical diagnosis: cancer of the stomach and cerebral hemorrhage. Autopsy: old cardiac infarct with aneurysm and parietal thrombo- sis. Severe arteriosclerosis, fresh cerebral softening. Chronic ulcer of lesser curv. of the stomach, 4 by 2 cm., penetrating deep into the pancreas. Multiple eroded blood vessels.
25	Hematemesis in hospital	♂	51	Eighth day	9 days	Admitted for lung and heart disease of long standing, obesity. No bleeding before admission. Autopsy: cardiac hypertrophy and universal arterio- sclerosis, localized bronchiectasia of the right lung. Chronic prepyloric ulcer, 2 by 3 cm., penetrating to the pancreas. Large eroded blood vessel.

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TABLE 1—*Concluded*  
Cause of death: Varied. Operation impossible or counter-indicated—*Concluded*

CASE NUMBER	MANIFESTATION OF HEMORRHAGE	SEX	AGE	TIME OF BLEEDING AFTER ADMISSION	INTERVAL BETWEEN ADMISSION AND DEATH	CLINICAL NOTES AND POST MORTEM FINDINGS
26	Hematemesis in hospital	♂	67	Third and fourth day	5 days	Transferred from a surgical department. Hypertrophy of the prostate and stricture of the urethra (no surgical intervention). Autopsy: Large embolus of the pulmonary artery, cardiac fibrosis, arteriosclerosis. Gastroenterostomy; three small chronic duodenal ulcers.
27	Hematemesis in hospital	♂	78	First day	1 day	Cachexia. Cancer of the liver, distinctly palpable. Autopsy: primary cancer of the liver with several metastases. Hypertrophy of the prostate, renal sclerosis and atrophy. Chronic duodenal ulcer, 2 by 2 cm. Large eroded blood vessel.
28	Hematemesis in hospital	♀	71	Fourth day	5 days	Hypertensive heart disease for several years, hemiparesis. Autopsy: severe universal arteriosclerosis, cardiac hypertrophy and fibrosis; cholecystitis. Chronic gastric ulcer, 1 by 1 cm., on the lesser curvature, threatening perforation. Gastroduodenal artery eroded.
29	Hematemesis in hospital	♀	75	First day	3 days	Severe arteriosclerosis and senility. Autopsy: universal, severe arteriosclerosis, cardiac fibrosis. Chronic duodenal ulcer, 1 by 1 cm., eroded blood vessel.
30	Hematemesis in hospital	♀	75	Fourth day	24 days	Admitted for severe heart failure of long standing, no bleeding before admission. Suspected of gastric cancer. Hb. 66-54 per cent. Autopsy: universal severe arteriosclerosis. Chronic duodenal ulcer, 2 by 3 cm.
31	Hematemesis in hospital	♀	78	First to third day	3 days	Senile, cachectic, irrational. No pains! Clinical suggestion: gastric cancer. Autopsy: Severe universal arteriosclerosis. Gastroenterostomy. Chronic duodenal ulcer, 1 by 1 cm., perforating to a large subdiaphragmatic abscess with passage to the left pleura. Another chronic gastric ulcer on the lesser curv. with threatening perforation. Acute pancreatitis.

B. 14 cases. These patients died either very shortly after admission or from other diseases than hemorrhage (embolism), or else there were complications so severe that the role played by hemorrhage as a cause of death is difficult to evaluate. Non-operative treatment is indicated in some cases, not in all, and any surgical intervention has been considered out of the question. Only 7 exhibited an eroded blood vessel, only 2 received blood transfusions, both died of embolism. Average age: about 70.

These classifications cannot be performed in full objectivity. Table 1 represents the writer's estimation, naturally open to criticism.

Dead as well as survivors are classified according to the mode of manifestation of the hemorrhage (hematemesis or melena) in relation to the time of admission.

(a) *No manifestation* means that the hemorrhage was only found at autopsy and was not visible *in vivo*.

(b) *Melena* means melena both before and after hospitalization. No hematemesis at any time.

(c) *Hematemesis before admission*. Before admission hematemesis, after admission only melena.

(d) *Hematemesis in hospital*. Before admission hematemesis or melena or no hemorrhage, after admission hematemesis.

Melena means group b. Hematemesis groups c and d.

### *Gross and Net Lethality*

Taking all dead the gross lethality rate is about 3.5 per cent. Taking those dying of exsanguination the net lethality rate is about 2 per cent. In Meulengracht's<sup>2</sup> series from the same department covering the period 1931-46 the lethality is slightly lower, 2.5 and 1.5 per cent respectively. The calculation has not been made in exactly the same way in both series, but the difference in lethality is mainly due to the fact that the number of persons in the more advanced age groups has been increasing at a rather amazing rate during the period in question. Patients with bleeding peptic ulcer are constantly getting older and so are those who die<sup>4</sup>. In Meulengracht's<sup>2</sup> series 50 per cent of the dead were 60 or more years of age, in the present series not less than 70 per cent (Table 1).

### *Material Analysed*

The material to be analysed is selected from the original material mentioned above. The analysis comprises: All fatal cases exhibiting peptic ulcer hemorrhage 40 or more years of age and all surviving cases of hematemesis and melena observed in hospital in patients 40 or more years of age, in whom a peptic ulcer was demonstrated by X-ray or at operation, and in whom the lowest hemoglobin percentage was less than 80.

This material may be characterized as a pure material of peptic ulcer cases with a definitely demonstrable ulcer and a certain loss of blood, presumably of not less than 1 liter. A condition considered necessary for surgical treatment by most writers: a demonstrated peptic ulcer, is present, and the age group below 40, in which deaths very seldom occur, has been left out of account.

As is well-known, a number of peptic ulcers heal quite rapidly during treatment. On the whole the patients of this material were not X-rayed until 3 weeks after admission. Some of them were not X-rayed, because a peptic ulcer had been demonstrated shortly before admission.

In 81 per cent of the cases included in the analysis a peptic ulcer was demonstrated during the stay in hospital for the particular hemorrhage, but in 19 per cent an ulcer had only been diagnosed by X-ray or at operation either shortly before or shortly after the hemorrhage.

The writer has formed an estimate of how many hemorrhages from real peptic ulcers may have escaped from the material because the ulcer may have healed prior to X-ray examination. A study was made of the diagnoses of 120 consecutive cases of "gastric hemorrhage" in patients aged more than 40 and in whom the lowest hb. was less than 80 per cent:

Definite ulcer (X-ray or operation):.....	84 = 70 per cent
Definite causes other than ulcer.....	13 = 11 per cent
No definite diagnosis.....	23 = 19 per cent

Of the last 23 cases a peptic ulcer was improbable in 6 (achlorhydria, lung-heart diseases etc.), whereas it was probable or not to be ruled out in 17 cases.

Accordingly the material analysed should comprise *at least*  $\frac{84}{84 + 17} = 85$  per cent of the actual number of bleeding peptic ulcers.

The criterion: hb. less than 80 per cent will not be dealt with further here. It serves *int. al.* to rule out the hemorrhages of no consequence in this connection, as they did not entail any deaths.

By means of the definitions given for the material analysed the writer has removed more than half of the original material, comprising only 1 death (No. 3 in Table 1) as statistically speaking of no consequence (Table 2).

The material analysed comprises 317 hemorrhages (288 patients), about 30 per annum. There are 30 deaths, 3 per annum, relatively as common among the males and females. Forty per cent of the dead were 70 or more years of age, 70 per cent 60 or more. The amount of the hemorrhage may be roughly characterized by stating that the lowest hb. was less than 60 per cent in two-thirds, less than 50 per cent in one-third of the survivors; 20 per cent were unconscious at least once before or after admission.

The *final analysis* is set out in Tables 3 to 8. In Table 4 the deaths not due to exsanguination (group B in Table 1) are left out. In Table 5 the lowest

hemoglobin percentage measured during the stay in hospital is used as a rough standard for the amount of blood lost in the survivors. The hemoglobin percentage was measured at frequent intervals. Shock indicates the combination of pale, cool extremities, cyanosis, a rapid pulse and low blood pressure. In Table 6 it is presumed that all the dead would have had a hemoglobin percentage of less than 50, if they had survived. This is only partly correct in the case of those listed in Table 1 B (deaths from embolism etc.). In Table 8 the reference numbers to Table 1 give the clue to the classification of fatal cases

TABLE 2  
*Analysed material in relation to entire material*

MATERIAL	NUMBER OF CASES	FATAL CASES	
		Total	Deaths from exsanguination
Original.....	About 850	31	17
Analysed.....	317	30	16
Rest (not analysed).....	About 500	1	1

TABLE 3  
*Lethality in relation to mode of manifestation and time of hemorrhage*

MANIFESTATION AND TIME OF HEMORRHAGE	NUMBER OF CASES	TOTAL NUMBER OF DEATHS		
		No. in Table 1	Number	Per cent
No manifestation.....	2	18, 19	2	100
Melena.....	119	1, 20, 21	3	2.5
Hematemesis before admission....	128	2, 22, 23, 24	4	3.1
Hematemesis in hospital.....	68	4-17, 25-31	21	31
Total.....	317		30	

among operable and inoperable. The complications in the 6 survivors considered inoperable were of exactly the same kind as in the fatal cases.

## RESULTS

The main result of this analysis is the setting up of a small group of hemorrhages with the easily recognizable sign of hematemesis in the hospital. The lethality of this group is so high and it comprises so large a number of those dying from exsanguination that criteria for surgical intervention with a view to hemostasis must be considered for this group.

## COMMENTS TO THE ANALYSIS

### *Lethality in Relation to the Mode of Manifestation and Time of Occurrence*

*No Manifestation.* The hemorrhages which do not manifest themselves *in vivo* are only met with in patients who are already so debilitated that they



can hardly be saved. They are rare and can be left out of consideration in the following.

*Melena.* There was no death from melena below the age of 60, and in the course of the 10 years investigated there was only one death from actual exsanguination (No. 1 in Table 1) which perhaps might have been saved. The few cases dying from or with a bleeding peptic ulcer without having had hematemesis are those suffering from mechanical obstructions in the stomach and duodenum, e.g. hour-glass stomach and pyloric stenosis or major adhesions to the neighbouring organs<sup>3</sup>. In these cases the melena is actually a masked

TABLE 4  
*Lethality from exsanguination in relation to mode of manifestation and time of hemorrhage*

MANIFESTATION AND TIME OF HEMORRHAGE	NUMBER OF CASES	DEATHS FROM EXSANGUINATION		
		No. in Table 1	Number	Per cent
Melena.....	117	1	1	<1
Hematemesis before admission....	125	2	1	<1
Hematemesis in hospital.....	61	4-17	14	23
Total.....	303		16	

TABLE 5  
*Profuse hemorrhages, shock, and blood transfusion in relation to the manifestation and time of hemorrhage*  
287 survivors

MANIFESTATION AND TIME OF HEMORRHAGE	SURVIVORS	LOWEST Hb LESS THAN 50%		HEMORRHAGIC SHOCK		BLOOD TRANSFUSION AT LEAST ONCE	
		No.	%	No.	%	No.	%
Melena.....	116	37	32	10	9	14	12
Hematemesis before admission.....	124	28	22	10	8	12	10
Hematemesis in hospital.....	47	32	68	28	60	26	55

hematemesis. In addition, the group contains patients who are so debilitated by other diseases, including loss of blood, that they are unable to vomit the blood (No. 1 in Table 1). Lastly, the patients may die from other causes than hemorrhage.

*Hematemesis.* Tables 3 and 4 show the great difference in the lethality among those whose hematemesis ceased upon admission and those whose hematemesis continued or began after admission.

*Hematemesis before Admission* (melena after). In these cases the lethality is as low as in those exhibiting only melena! This is partly because some of these "hematemesis" have been very slight or false (see Table 5), but primarily because the actual hemorrhage has ceased at the time of admission and

is not repeated. Exsanguinated patients of this kind and exsanguinated melenas are just the cases for the Meulengracht regimen and similar non-starving treatments.

Those who die from hematemesis prior to admission (melena after) are partly patients who die from other causes than hemorrhage (embolism, Table 1 No. 22 and 23), or from hemorrhage plus complications (Table 1 No. 24),

TABLE 6  
*Lethality in relation to manifestation and time of hemorrhage*  
Profuse hemorrhages (hb. less than 50%)

MANIFESTATION AND TIME OF HEMORRHAGE	WHOLE (ANALYSED) MATERIAL			SURVIVORS + DEATHS FROM EXSANGUINATION		
	Number of cases	Fatal cases		Number of cases	Fatal cases	
		No.	%		No.	%
None, melena, hematemesis before admission . . .	74	9	12	67	2	3
Hematemesis in hospital . . . . .	53	21	40	46	14	32
Total . . . . .	127	30	24	113	16	14

TABLE 7  
*Lethality and age*  
Hematemesis in hospital

AGE GROUPS	WHOLE MATERIAL			SURVIVORS + DEATHS FROM EXSANGUINATION		
	Number of cases	Fatal cases		Number of cases	Fatal cases	
		No.	%		No.	%
40-49	21	2	10	21	2	10
50-69	35	11	31	33	9	27
70 and over	12	8	67	7	3	43
	47	19	40	40	12	30
40 and over	68	21	31	61	14	23

partly patients who die shortly after admission and who no longer have the strength to vomit the blood because of exsanguination (Table 1 No. 2).

The last-mentioned category brings up a social question. In Copenhagen most major hemorrhages are hospitalized so quickly that those who die from hemorrhage in hospital have got blood and strength enough left to yield a hematemesis after admission. In other places where the distance to the hospitals is longer, where there are other customs and where social care is perhaps not as wide-ranging, it is possible that there would be more of the type of case which is completely exsanguinated and who is barely able to yield a melena

after admission before he dies. It is not known how common an occurrence this is in other localities. Patients of this type are very difficult to save.

*Hematemesis in Hospital.* Nearly all the dead had hematemesis in hospital (Table 1), i.e. 22 of 31 or 70 per cent. It is apparent from Table 1 A that no less than 15 of 17 or 90 per cent of those dying from exsanguination exhibited this sign. The above-mentioned study of a post-mortem material showed that 85 per cent of the dead had exhibited hematemesis. The present study confirmed this, and now it can be stated that the hematemesis takes place after hospitalization.

A comparison of Tables 1 A, 2 and 4 reveals that the writer has succeeded in setting up a small group of 61 patients who make up less than 10 per cent of the total number of bleeding cases, (about 850), but who make up 14 out of 17 or 82 per cent of those dying from exsanguination. Among the remainder

TABLE 8  
*Lethality of operable and inoperable cases in different age groups*  
Hematemesis in hospital

AGE GROUPS	OPERABLE CASES				INOPERABLE CASES				
	Number	Deaths			Number		Deaths		
		No.	%	No. in Table 1	Total	Survivors	No.	%	No. in Table 1
40-49	18	1	5	4	3	2	1	33	13
50-69	27	8	6 22	5-8, 11, 12 9, 10	8	3	11	5 63	14-16, 25, 26 17, 27-31
70 and over	5								
	32	2	40	25	15	4	6	86	
40 and over	50	9	18		18	6	12	67	

of the original material there are only 3 deaths from exsanguination, a net lethality tending towards 0.

*Amount of Blood Lost in Relation to Mode of Manifestation and Time of Hemorrhage*

According to Table 5 the survivors in the group: hematemesis in hospital were those who most often had large hemorrhages and hemorrhagic shock and who most frequently received blood transfusion. It is evident that this group on the whole has had extremely serious hemorrhage, but this is not only because the loss of blood is usually great. Table 6, only comprising major hemorrhages, reveals a marked difference in the lethality of hematemesis in hospital and the other modes of manifestation. It is much more dangerous to lose blood by a hematemesis than by melena, even if the amount lost in either case is large and about the same, because the loss is more rapid in hematemesis.

A comparison of Tables 3 and 4 with Table 6 affords a confirmation of this. The lethality rate for all major hemorrhages (hb. less than 50 per cent) is 24 per cent (Table 6, bottom), but for hematemesis in hospital (hb less than 80 per cent) 31 per cent (Table 3). Including only those who died from exsanguination, we arrive at a lethality rate of 14 per cent for all major hemorrhages (Table 6, bottom), but of 23 per cent for hematemesis in hospital (Table 4).

#### CRITERIA FOR SURGICAL INTERVENTION

According to the results of the analysis surgical intervention might be proposed for the group of hematemesis in hospital. In this group the lethality increases with advancing age, as might be expected (Table 7).

In the age group 40-49 the lethality rate is not so high that operation is indicated for the entire group, particularly as the 2 fatal cases did not receive blood transfusions for various reasons.

The age group 50 and over has a lethality rate from exsanguination of 30 per cent (Table 7) and this seems to indicate surgical treatment of all cases in the acute stage, provided that there are no complications which counterindicate operation.

Then the criteria tentatively proposed for surgical intervention in peptic ulcer hemorrhage run as follows: Age 50 or more, hematemesis in hospital proven peptic ulcer.

#### DISCUSSION OF THE CRITERIA SET UP

There is no way of knowing beforehand in which cases the hemorrhage is going to stop. In the age group 50 to 69 the chances are about 1:2 that the hemorrhage will continue, and in the age group above 70 almost 1:1 (Table 7). In other words, in these age groups (50 or more years) one should not await the reply of nature to the question whether the hemorrhage will stop, but operate in all cases as soon as a peptic ulcer has been demonstrated.

According to the definition used for selection of the analysed material the loss of blood in hematemesis should be of such an amount that the hemoglobin falls to less than 80 per cent, if the patient survives. In other words, the loss of blood need not be great, and actually one may leave the quantity out of ones calculations altogether. If the lethality rate is calculated only on the basis of the survivors with a hemoglobin percentage of less than 50 or of those who exhibited a hemorrhagic shock, there is an increase (Table 6), because the group now is smaller. At the same time the operative lethality rises, because now the patients are more difficult to operate upon. The pre-operative treatment and the surgeon's skill must decide the magnitude of hemorrhage and degree of debility at which operation is indicated. Among patients even with only 1 hematemesis in hospital, past 50 years of age with a demonstrable peptic ulcer the lethality is so high that it probably pays to operate in all cases with-

out wasting valuable time in waiting to see whether the hemorrhage is repeated, persists or ceases. It does not change matters that the surgical cases are perhaps increased up to 15 per cent, when early roentgenography is employed. Experts in gastric surgery may perhaps temporize in order to avoid operating some of the cases in the acute stage, in which the hemorrhage will prove to cease spontaneously at last. Lacking surgeons with routine in gastric surgery, the wisest course is no doubt to continue with non-operative treatment. (v.i.)

If surgery is decided upon the cardinal point is to operate as quickly as possible after the first hematemesis in hospital. It is a question of acting immediately, as soon as the criteria have been fulfilled, meaning in practice as soon as the ulcer has been demonstrated and other diseases excluded. As a rule most patients do not die until they have had several hemorrhages in hospital, and it is apparent from Table 1 A that there may be an interval of several days between the first hematemesis in hospital and death. A consequence of the criterion set up is that several patients will now arrive at the operating table at an earlier stage of the hemorrhage. At this time some of the patients will probably not be or not have been particularly affected by their hemorrhage. In this way one of the most important conditions for a low operative lethality has been fulfilled<sup>5, 6, 7, 8, 9</sup>.

The easily demonstrable criterion of hematemesis supersedes more difficult estimations of the persistence of the hemorrhage and the amount of blood lost. This is of particular importance in view of the small number of patients to be operated upon. Now our attention can be concentrated on the hemorrhages which involve a particular risk. Any person 50 or more years of age exhibiting hematemesis in hospital is in the danger zone. The time of this hematemesis is of no consequence, and practically speaking the same applies to the amount of blood lost, and thus such persons ought to be submitted to appropriate diagnostic measures at once.

### *Surgical or Medical Treatment*

We now have to continue the discussion on purely practical lines and proceed to estimate the problem on the basis of the figures in Table 8. As soon as one has realized the poor prognosis in this group of patients, when left to conservative treatment, and feels convinced of the justification of surgical intervention in all operable cases, the most important question remains whether the individual case presents general, definite contra-indications to surgery or not. This decision determines the method of treatment, and it should be the result of a collaboration between the internist and the surgeon, paying due regard to the high lethality in conservative treatment and—equally important—the surgeon's skill in performing difficult gastric operations. Table 1 shows that such contra-indications are often found among those who die during conservative treatment. As apparent from Table 7 and 8 there was a total of 47 patients in the group and only 32 of them were deemed operable, i.e. only two-thirds. The lethality in non-operative treatment is then 25 per cent in the operable cases (Table 8), and this is the lethality to be reduced by means of surgical intervention. Is it possible? The writer is not in possession of a material to show it, and the literature does not appear to offer any large materials to decide the

question, because they are not grouped according to age. On the basis of calculations made in a few small series (Bohmansson<sup>10</sup>, Metheny & Green<sup>11</sup>) the writer feels that it might not be impossible to operate in the *operable* cases with a 10 per cent lethality, provided that early surgery is done in fully equipped departments with experienced surgeons and an ideal collaboration between internist and surgeon.

In our material 32 patients are left for operation during a period of 10 years, i.e. 3 per annum, <5 per cent of all cases of bleeding peptic ulcer or ulcer disease in the original material. Treated non-operatively 8 of 32 or 25 per cent will die from exsanguination (Table 8). If our surgeons can operate upon these 32 patients with a lethality rate of say 10 per cent, 5 patients will be saved from death from exsanguination in the course of 10 years. The lethality rate from exsanguination (Table 7) will fall from 30 to about 17 per cent. The number of deaths from exsanguination in the entire material will fall from 17 to 12 during the 10-year period and the net lethality in Department B will be reduced by about 30 per cent.

This goes to show that the numbers are not high within each individual department and that much work must be done and much ability is required in order to save but 1 patient every other year. The problem: surgery or not, can therefore not be solved generally, but it must be decided upon at each hospital, paying regard to the local circumstances. Where it has or will be decided to attempt to reduce the lethality in this group by surgery, centralization of the treatment in a few departments is desirable.

As mentioned before surgery at a late stage of the hemorrhage is attended with an extremely high lethality, as high as found in conservative treatment of inoperable cases (Table 8), and surgery at an early stage seems to be the only way in which surgery can lower the lethality of this group. What has been said above urges to either a consistent conservative treatment of all within the group or a consistent surgical treatment of all operable cases as soon as the criteria have been fulfilled and as far as possible to avoid intermediate methods like operation at a late stage on vital indication after a long time's conservative treatment. (Allen<sup>6</sup>)

It is too early to evaluate the criteria set up here in relation to those established earlier. Patients who are submitted to operation according to the criteria set out in this paper will as a rule also be operated upon according to the criteria set up by others during recent years, only the dangerous hemorrhages will now be easier to diagnose and the operation will in some cases be performed earlier. On the other hand the proposed criteria: age group 50 or more years, hematemesis in hospital, demonstrable niche, select for surgery only 12 of 17 or 70 per cent of those dying from exsanguination. The treatment of the remaining 5 cases (2 operable) must be according to the principles previously set up by others, which means individualizing.

There is almost general agreement that operation is very seldom advisable in any case less than 40 years of age. (Since 1931 only 1 patient in this age group has died from bleeding peptic ulcer in Medical Department B). As to the patients in the age group 40 to 49 with hematemesis in hospital, the treatment must be individual, and a second bleeding might be awaited, before operation is decided upon.

Only a few patients die from melena, and operation is only contemplated when

melena has occurred repeatedly as a real new hemorrhage in the department, unless the patient belongs to the group who are admitted greatly exsanguinated from hematemesis. As mentioned above, this is rare in Copenhagen. Severe pain, stenosis or gastro-jejunal ulcer enhance the indication for operation. In our material these 3 conditions as well as perforation raise the lethality considerably in contradistinction to earlier hemorrhage and earlier operations on the stomach<sup>9, 10</sup>. It is the writer's experience from post mortem materials that patients who during the stay in hospital have repeated hemorrhages manifesting themselves exclusively in the form of melena rather frequently present technical difficulties as regards surgery, because there are often local complications (masked hematemesis). It is not "normal" to die from melena.

### *Lethality Statistics*

It is actually impossible to compare the effectiveness of the various methods of treatment, because most statistics are—to say the least—insufficient. All statistics of lethality ought to fulfill the following minimum requirements: Only comprise hemorrhage from definite ulcers, be classified into age groups, be classified into groups of hematemesis and melena respectively before and after admission, state the amount of blood lost in connection with the rate of bleeding, be grouped into complicated and uncomplicated cases, and contain adequate information about all deaths.

The value of a particular treatment is, however, sufficiently characterized by the lethality it involves among patients 40 or more years of age who exhibit hematemesis in hospital, who have a definite peptic ulcer, and in whom the hemoglobin percentage is less than 80 per cent in the survivors. The material should be divided into age groups, into complicated and uncomplicated cases, and should contain details about all deaths.

The lethality from hemorrhages falling outside the group defined is very slight under the conservative treatment in use at the present time, and it would be difficult to prove a reduction in this lethality. On the other hand—as demonstrated above—the group we are dealing with has a high lethality. It can be set up by simple means and therefore everywhere.

In conclusion the writer wishes to mention that the easily recognizable criterion: hematemesis in hospital, proposed in this paper may appear to select rather "mechanically" and perhaps at first glance seem somewhat unbiological, leaving no great space for individualization. However, it appears to be the logical consequence of definite biological observations: the lethality from bleeding peptic ulcer depends int. al. on the rapidity of the hemorrhage, its magnitude and persistence, which again depend on the nature of the source of the bleeding. Hematemesis in hospital is here an essential sign, and in connection with a knowledge of the patient's age and the source of the hemorrhage being a peptic ulcer, it is "a really trustworthy guide to prognosis at an early stage".

### SUMMARY AND CONCLUSIONS

In an earlier analysis of post-mortem material it was demonstrated that in cases of gastric and duodenal ulcer hematemesis is a more dangerous form of

bleeding than melena. The writer maintains that hematemesis is a symptom of *rapid* bleeding. In 85 per cent of fatal cases there was hematemesis, and in 15 per cent melena. In 85 per cent of the fatal cases an eroded blood vessel was demonstrable. In 90 per cent the lesion was a real peptic ulcer. Ninety-four per cent of the cases were aged over 40 years, 82 per cent were over 50 years of age.

This paper is a clinical analysis of some 850 cases of bleeding peptic ulcer and ulcer disease treated according to Meulengracht's principles of prompt, free and frequent feeding and blood transfusion during the period 1938-1948. This analysis confirms the poor prognosis in cases of hematemesis, when it occurs after hospitalization. Seventy per cent of all fatal cases and ninety per cent of those dying from exsanguination had hematemesis in the hospital.

Taking the entire material the mortality from exsanguination was about 2 per cent. The material is divisible into a large group with an absolutely favorable prognosis and a small group, further described below, with a poor prognosis.

In the large group, comprising about 800 cases, the mortality from exsanguination was less than 1 per cent (5 deaths). In the small group, comprising 40 patients, the mortality was 30 per cent (12 deaths). Less than 10 per cent of all cases of bleeding peptic ulcer, but 70 per cent of all dying from exsanguination are to be found within this small group.

The small group with the high mortality consist of persons with ulcer aged over 50 years, with hematemesis in the hospital.

Of the 40 patients in this group only 32 were operable, i.e. 3 per annum. Of them 8 died during the conservative treatment, a lethality of 25 per cent. The possibility of reducing this lethality by surgery is discussed. In some places—where specialized surgeons are available—surgery may be the principal method of treatment for this small group. Provided that surgical measures are not contra-indicated, all patients in the group set up should then be submitted to operation immediately after the first hematemesis in the hospital. Another hemorrhage should not be awaited, and therefore many operations will be performed at an early stage of the hemorrhage.

Principles of mortality statistics in bleeding peptic ulcer are discussed.

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## HEPATITIS WITHOUT JAUNDICE IN INFECTIOUS MONONUCLEOSIS\*

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### INTRODUCTION

Infectious mononucleosis has long been known to be complicated by jaundice in a significant per cent of cases<sup>1, 2</sup>. Punch biopsies of the liver of such patients have shown this complication to be due to an acute focal hepatitis<sup>3, 4</sup> and clinical support for this finding has been given by the presence of abnormal tests of liver function in jaundiced patients with infectious mononucleosis<sup>2</sup>. In patients with this disease who were not jaundiced, aspiration biopsy of the liver<sup>5</sup> and autopsy examinations<sup>6, 7, 8</sup> likewise have revealed a picture of focal hepatitis. In 1946 Cohn and Lidman<sup>9</sup> reported abnormal liver function in 15 consecutive cases of infectious mononucleosis without jaundice and they attributed these findings to an acute hepatitis. Subsequently, liver involvement in such patients has been reported in 19 cases by Carter and MacLagan<sup>10</sup>, in 29 of 31 cases by Gall<sup>11</sup>, in 19 consecutive cases by DeMarsh and Alt<sup>12</sup> and in 17 of 19 patients by Evans<sup>13</sup>. The purpose of this paper is to report the findings of 20 cases of infectious mononucleosis without jaundice in which liver function tests were performed during the course of the disease.

### METHODS

Since the fall of 1945 all cases of infectious mononucleosis reporting to the Student Health Service, Northwestern University, Chicago, Illinois, have routinely been studied for evidence of liver involvement. Sixteen consecutive cases of infectious mononucleosis, studied since completion of the series of DeMarsh and Alt, are included in this report. In addition, Cases # 6, 7, 13 and 15 in whom liver function tests were made were private patients admitted to Passavant Memorial Hospital. In all cases the clinical course, blood studies and heterophile antibody tests established without doubt the diagnosis of infectious mononucleosis. Although serial tests of liver function were made on more than one-half of the patients, to conserve space, only the most abnormal values have been recorded in Table I with a recording, also, of the number of days after the onset of symptoms that these tests were performed.

Heterophile antibody tests were performed by the method of Davidsohn<sup>14</sup> without differential absorption. Agglutination in a titer of 1:224 or over was considered diagnostic of the disease.

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TABLE I  
Liver function tests in 20 cases of infectious mononucleosis\*

CASE, SEX, AGE	DATE OF ONSET OF SYMPTOMS	HETEROPHILE ANTIBODY TEST	ICTERUS INDEX	CEPHALIN CHOLE- STEROL FLOCCULA- TION		BROMSULFA- LEIN RETENTION	LIVER†	SPLEEN†	SYMPTOMS
				24 hr.	48 hr.				
1, F, 22	10-19-46	1:1792 (7)	7 u (6)	****	**** (7)	20% (6)	P	P	Mod.
2, M, 21	1-21-47	1:448 (14)	8 u (4)	****	**** (4)	20% (4)	P	P	Mod.
3, M, 21	1-31-47	1:896 (19)	10 u (4)	*	*** (26)	8% (4)	P	P	Mod.
4, F, 20	2- 1-47	1:896 (30)	—	0	* (11)	—	NP	NP	Mild
5, F, 27	2- 5-47	1:224 (21)	7 u (13)	***	**** (8)	—	NP	NP	Mild
6, F, 29	5-16-47	1:224 (16)	5 u (13)	****	**** (13)	4% (13)	NP	NP	Mod.
7, M, 40	5-20-47	1:896 (15)	10 u (17)	*	** (17)	—	NP	NP	Mod.
8, M, 24	6- 5-47	1:224 (6)	4 u (12)	***	**** (12)	10% (12)	NP	NP	Sev.
9, M, 22	6-16-47	1:3584 (8)	4 u (8)	—	—	10% (8)	P	P	Mod.
10, M, 28	7-29-47	1:7168 (20)	—	0	0 (20)	1% (24)	NP	NP	Mild
11, M, 23	10- 3-47	1:448 (11)	—	*	*** (11)	7% (11)	NP	NP	Mod.
12, M, 21	10-17-47	1:224 (5)	—	0	** (7)	3% (10)	NP	NP	Mod.
13, F, 19	2- 1-48	1:1792 (10)	19 u (10)	****	**** (10)	56% (10)	P	P	Sev.
14, M, 24	2-15-48	1:448 (12)	—	***	**** (12)	9% (12)	NP	P	Mild
15, M, 19	3- 1-48	1:1792 (8)	7 u (8)	0	* (11)	20% (8)	NP	†	Mod.
16, M, 23	3-23-48	1:896 (8)	—	*	** (22)	0% (4)	NP	P	Mild

TABLE I—Continued

CASE, SEX, AGE	DATE OF ONSET OF SYMPTOMS	HETEROPHILE ANTIBODY TEST	ICTERUS INDEX	CEPHALIN CHOLES- TEROL FLOCCULA- TION		BROMSULFA- LEIN RETENTION	LIVER†	SPLEEN†	SYMPTOMS
				24 hr.	48 hr.				
17, M, 25	4- 5-48	1:3594 (8)	—	**	*** (9)	23% (9)	NP	P	Mod.
18, M, 23	4-24-48	1:7168 (11)	—	***	*** (11)	38% (11)	NP	NP	Mod.
19, M, 36	4-29-48	1:896 (13)	—	****	**** (5)	35% (5)	P	P	Mod.
20, M, 20	5-11-48	1:448 (3)	—	****	**** (13)	30% (11)	P	P	Sev.

\* Figures in parentheses indicate number of days after onset of symptoms.

† P indicates palpable; NP indicates not palpable.

† Spleen removed one month prior to onset of symptoms.

Tests of liver function included the cephalin-cholesterol flocculation test, bromsulfalein test and the icterus index. The cephalin-cholesterol flocculation test was performed by the method of Hanger<sup>15</sup> as modified by Neefe and Reinhold<sup>16</sup>. Values of 2 plus or more at 48 hours were considered abnormal<sup>17</sup>. In the bromsulfalein excretion test 5 mg. of the dye per kilogram of body weight was given intravenously and blood was withdrawn 45 minutes later. Retention in excess of 4 per cent, as determined photoelectrically, was considered abnormal<sup>17</sup>. Normal values for the icterus index range from 4 to 7 units<sup>18</sup>.

## RESULTS

On the basis of the liver function tests performed, 16 of the 20 cases revealed definite evidence of hepatic involvement. Of the remaining 4 cases, 2 showed possible evidence of liver dysfunction and in 2 cases such evidence was absent.

The cephalin-cholesterol flocculation test was performed in 19 patients and was positive in 13. Bromsulfalein excretion was determined in 17 patients and showed abnormal retention in 13. Of the 16 cases showing definitely abnormal values, both tests revealed liver involvement in 11. Of the 5 cases in which both tests were not positive, Cases # 5 and 6 revealed a positive cephalin-cholesterol flocculation test. Bromsulfalein excretion was not determined in the former and showed only 4 per cent retention in the latter. There was abnormal retention of bromsulfalein in Cases # 9 and 15, whereas the cephalin-cholesterol test was not performed in the former and was negative in the latter. In Case # 7 the bromsulfalein test was not made and the cephalin-cholesterol flocculation test was a 2 plus reaction. However, the urine urobilinogen was 10.8 Erhlich units and thus confirmed the presence of liver involvement<sup>19</sup>.

In addition to the 16 patients in whom definitely abnormal liver function was observed, 2 cases were thought to have possible liver involvement. In Case # 12 there were 3 per cent bromsulfalein retention and an initial 2 plus cephalin-cholesterol flocculation test. One week later the latter test was negative. Case # 16 revealed no retention of bromsulfalein and only a 2 plus cephalin-cholesterol flocculation in a single determination of each test. In both patients the disease was mild. In only 2 patients, Cases # 4 and 10, were the liver function tests completely normal.

The icterus index was determined in 11 patients and was slightly elevated in 4. In Case # 13 the icterus index showed a transient rise to 19 units. However, subsequent tests ranged from 13 to 10 units. None of the patients was jaundiced.

The liver was palpable in 7 of 20 patients (35 per cent), all of whom showed definite changes in liver function. The spleen was palpable in 10 cases. Case # 15 had had a splenectomy for traumatic rupture of the spleen in a serious accident one month prior to the onset of symptoms of infectious mononucleosis.

#### DISCUSSION

In infectious mononucleosis without jaundice the alteration in liver function usually becomes evident within 2 weeks of the onset of symptoms. It must be emphasized that this hepatic involvement may be of short duration and that unless serial tests of liver function are made, significant alterations may be missed. Of the patients in the present series who showed questionable evidence of liver involvement, in Cases # 12 and 16, the bromsulfalein excretion test was performed only once and was normal. In Case # 12 the cephalin-cholesterol flocculation test was performed twice, whereas in Case # 16 this test was made only once. In both, the results were 2 plus in 48 hours and were interpreted as possible evidence of disordered liver function. In Case # 4 two cephalin-cholesterol flocculation tests were normal and the bromsulfalein retention was not determined. In Case # 10 each test was performed only once with normal results. Had more frequent tests been made, it is possible that one or more of these patients would have shown more positive evidence of liver involvement. It is, of course, possible that the liver was not involved at all or involved so slightly as to produce no change in the function tests chosen.

It has been suggested that the changes in liver function occurring with infectious mononucleosis are no different than those which might be observed in any virus disease of comparable severity. However, Evans<sup>13</sup> performed cephalin-cholesterol flocculation tests on 22 consecutive patients with simple upper respiratory infections as a control for his series of cases of infectious mononucleosis. In all 22 controls the test was repeatedly negative whereas

in 17 of 19 cases of infectious mononucleosis the test was positive. Along with the pathological picture of the liver in infectious mononucleosis, this observation should establish the specificity of the liver involvement.

Determination of liver involvement in infectious mononucleosis may be of importance in the diagnosis as well as the management of the disease. Not infrequently the heterophile antibody test and the differential blood count remain normal even several days after the onset of high fever. In such cases the occurrence of abnormal liver function will be indirect evidence of this disease, since it is known that in mild virus infections the liver is not involved. In regard to the management of such patients, it would seem unwise for a patient to return to unlimited activity before the liver function tests show normal or near-normal levels.

Including the present cases with those previously recorded, abnormal liver function in infectious mononucleosis without jaundice has been observed in 115 out of 123 cases (93 per cent). On the basis of the previous reports of pathological changes in the liver of such patients, the hepatic involvement is probably due to an acute hepatitis. The almost constant occurrence of liver involvement in infectious mononucleosis further emphasizes the generalized nature of this disease.

#### SUMMARY

In 20 cases of infectious mononucleosis without jaundice 16 were found to have definitely impaired liver function as determined by the cephalin-cholesterol flocculation and the bromsulfalein excretion tests. Of the remaining 4 cases, 2 had possible, and 2 had no evidence of liver involvement but liver function tests were too infrequent to exclude liver disease. Including this series, abnormal liver function now has been recorded in 115 of 123 cases of infectious mononucleosis without jaundice. The liver dysfunction has been attributed to an acute hepatitis.

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## BACTERIOLOGICAL EXAMINATION OF THE DUODENAL CONTENT WITH THE AID OF A SPECIAL TUBE

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In his monograph (Gastroenterology, Vol. 3, 1946) Bockus remarks about the bacteriological examination of bile which has been obtained through the duodenal tube: "Unfortunately no technique has been developed which definitely eliminates the factor of contamination of bile withdrawn through a duodenal tube." After a survey of the literature in this field, one must agree with this author. Many investigations of the bacteriology of the bile and the duodenal juice in healthy and pathological subjects have been published, but they all suffer from an essential error: the technique which has been used has not allowed the investigators to draw conclusions about the bacteriology of the material obtained. Only in a few cases, in which it has been possible to show a special intestinal flora, has the investigator been justified in assuming that the bacteria found came only from the duodenal content. The few reliable bacteriological investigations which have hitherto been published deal with surgical cases in which bile has been sent for bacteriological examination in connection with operations on the gall ducts or gall-bladder. These special surgical cases have not permitted of general conclusions about the bacteriology of the duodenal juice and bile in the healthy and pathological states.

### THE AUTHOR'S OWN EXAMINATIONS

In 1944 the author published a method which in certain conditions enabled one to free the duodenal juice from contaminations. This "sterile-tube" was tested (33), and was shown to function satisfactorily. Not until this year, however, has it been tested on clinical material. Briefly the method is as follows:

The tube which is to be pushed into the stomach and duodenum is sterile. This is ensured by using an outer larger tube which has two channels. Through one of these channels runs the duodenal tube. When these two tubes have been sterilized, the lower end of the larger outer tube is closed by a collodion membrane. The larger tube with the finer one inside, is then pushed down to the region of the cardia.

With the help of a subcutaneous histamine injection or the injection of a hydrochloric acid solution in the stomach, the content of the stomach is acidified. In this acid gastric-content all ordinary forms of bacteria are killed. When the double tube has been pushed down as above, suction is made both



in the mouth and in the esophagus. Then the collodion membrane is perforated by pushing down the finer inner tube with the larger outer one fixed to the cheek.

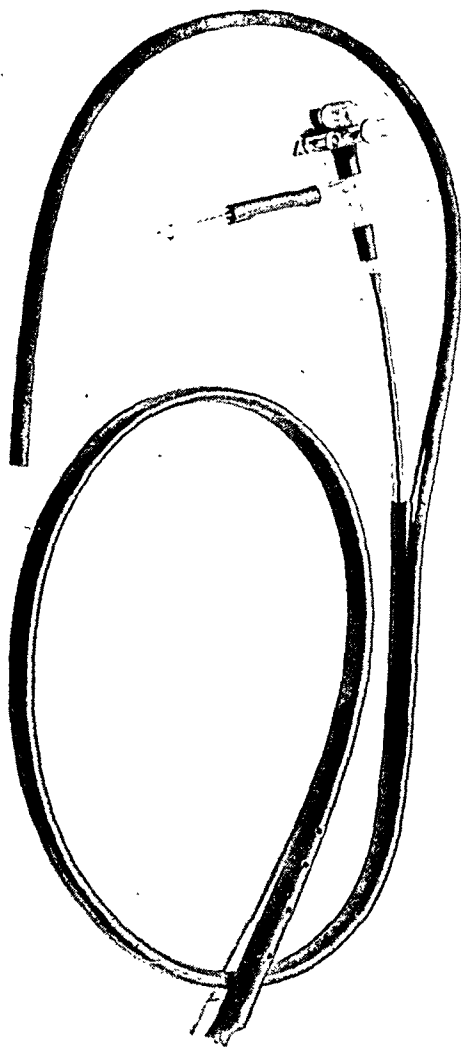


FIG. 1. THE TUBE

On the lower part holes for esophageal suction. On the upper part the finer duodenal tube.

The sterile finer tube (duodenal tube) is now in the acid-sterilized content of the stomach. The patient lies on his right side and the stomach content is sucked up for bacteriological examination as a control. The duodenal tube is provided with a metal tip which is attached by a 10 cm. long silk thread to the olive. This is to facilitate the passage to the duodenum and the retaining of the tube there.

The patient is instructed to lie on his right side and the duodenal tube is

fed successively deeper and deeper. The passing of the tube to the duodenum is controlled by blowing air through the duodenal tube and the at-

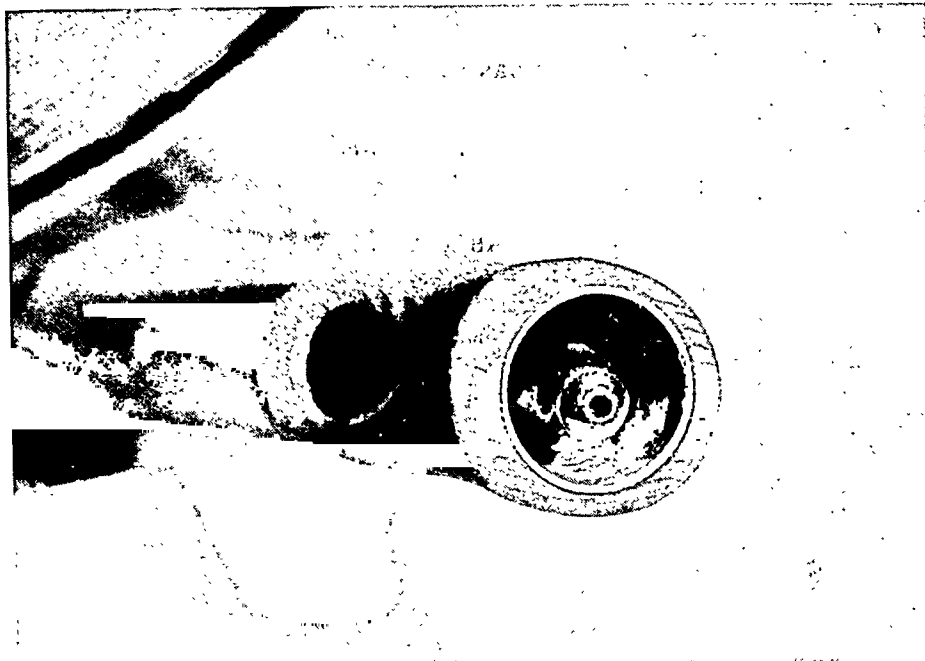


FIG. 2. THE LOWER PART OF THE TUBE. INSIDE THE DUODENAL TUBE

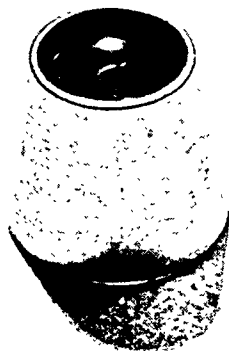


FIG. 3. THE COLLODION MEMBRANE ON THE UPPER PART OF A LITTLE SILVER CONE  
The membrane is obtained by dipping the cone in a solution of collodion, ether and ethyl-alcohol.

tempt to get it back by suction with a syringe. The pH of the bile-stained duodenal juice is measured, and when one is sure one has got pure duodenal juice, one injects sterile 20%  $\text{MgSO}_4$  through the tube to get bile from the

gall-bladder. *The result of the bacteriological cultivation is taken into consideration only in those cases in which the cultivation of the gastric juice was negative.* This gives a guarantee for an effective barrier to contaminations from the upper digestive tract. By using at the same time a suction device for the mouth and esophagus, it has been attempted further to reduce this risk.

The material which was sucked up was passed directly into sterile bottles, the content of which was then sent for bacteriological cultivation. This

TABLE 1

CASE NO.	GASTRIC JUICE				DUODENAL JUICE					ESOPH.	SALIVA
	Time for suction	Ml.	HCl.	Tot. ac.	Before MgSO <sub>4</sub>		After MgSO <sub>4</sub>		Time for suction	Ml.	Ml.
					Ml.	pH	Ml.	pH			
	<i>min.</i>								<i>min.</i>		
1	100	280	92	102	15	7	5	7	20	50	80
2	170	465	98	114	10	3-4	70	3-4	30	85	130
3	105	119	126	134	94	7.5	32	6.5	90	20	35
4	70	—	100	116	60	7	50	6	55	30	120
5	15	21	96	104	26	5	12	7	70	0	120
6	40	106	30	76	21	5	56	6	50	20	30
7	60	145	90	100	26	5	45	6	120	25	12
8	30	54	52	70	8	7	28	7	85	65	130
9	65	115	94	104	35	7	40	7	40	3	220
10	125	235	88	102	25	5	30	7	25	0	310
11	45	112	30	46	22	7.5	84	7.5	65	10	4
12	40	105	56	68	20	6	25	7	105	2	35
13	45	114	34	60	14	7.5	16	5.5	90	0	60
14	95	90	55	85	12	5.5-6	42	7	55	6	23
15	60	62	50	65	46	6	14	6.5	130	120	65
16*	—	85	48	72	18	7	67	7	—	15	100
17*	35	45	64	74	20	6	30	7	65	—	130
18*	155	42	80	84	65	7.5	45	7	60	50	82

\* In these cases 50 ml. of dilute hydrochloric acid was injected in the stomach.

has included both aerobic and anaerobic cultivations. 18 cases have been examined with this technique.

As we were making an orientative examination with a new method, the cases have to some extent been chosen arbitrarily, but it was attempted also to include cases with diseases in the bile ducts and gall-bladder and cases with achlorhydria, as in these cases an abnormal duodenal flora might be expected.

Tables 1 and 2 are records from these aspirations. One finds that gastric juice has been sucked up during periods varying from 15 min. to 170 min. This is also the time it has taken for the duodenal tube to reach the duodenum. The average time is 73 min. As compared with other methods, this is an unusually short period. In the cases 16, 17 and 18 there was

achlorhydria, for which reason 50 ml. of a sterile solution of 50 drops of acid. hydrochloric. dil. was in these cases squirted through the tube when this was in the stomach. This solution proved to be able to effect sterile conditions in the stomach. The fractions obtained from the duodenum proved to have a pH of about 5-7, with the exception of one case, in which the pH was only 3-4. X-ray control showed the duodenal tube to be in the duodenum also in this case. The suction in the esophagus introduced by the

TABLE 2

CASE	DIAGNOSIS	RESULTS OF BACTERIOLOGICAL EXAMINATION		
		Gastric Juice	Duodenal juice	
			Before MgSO <sub>4</sub>	After MgSO <sub>4</sub>
1	Duodenal ulcer	No growth	No growth	No growth
2	Duodenal ulcer	No growth	No growth	No growth
4	Psychoneurosis	No growth	No growth	No growth
4	Gastric ulcer	No growth	No growth	No growth
5	Colitis	No growth	No growth	No growth
6	Colitis	No growth	No growth	No growth
7	Psychoneurosis	No growth	No growth	No growth
8	Psychoneurosis	No growth	No growth	No growth
9	Late lues	No growth	No growth	No growth
10	Hyperbilirubinaemia (physiologic)	No growth	No growth	No growth
11	Pleuropneumonia	No growth	No growth	No growth
12	Cholecystitis chron.	No growth	B. coli	B. coli
13	Cholecystitis chron.	No growth	B. coli	B. coli
14	Cholelithiasis	No growth	No growth	Str. faecalis
15	Gastroenteritis	No growth	Str. faecalis + β-hemolyt.	Str. faecalis
16	State after subtotal gastrectomy (Achyilia gastrica)	No growth	Staph. pyog.	Staph. pyog.
17	Pernicious anemia	No growth	B. coli	B. coli
18	Pernicious anemia	No growth	B. coli	Staph. pyog.

author proved to be particularly valuable, as may be seen from the figures concerning the quantity of secretion which was sucked up from the esophagus.

This arrangement was especially valuable in cases in which despite instructions to the contrary the patient could not help swallowing saliva, or was too unintelligent to manage the saliva pump. In cases 1, 2, 3, 6, 7, 8, 11 and 18 there are thus quantities of secretion in the esophagus which exceed 50% of the simultaneously sucked up saliva (from the cavity of the mouth).

#### BACTERIOLOGICAL EXAMINATION

In the bacteriological cultivation all the fractions from the stomach were sterile. In the 18 cases examined the duodenal juice was sterile in 11 cases.

In 4 cases there was a coliflora, in one case only staphylococcus pyogenes and in 2 cases streptococcus faecalis (in one of these cases also  $\beta$ -hemolytic streptococci). A closer examination of the sterile cases shows in this group cases of duodenal and gastric ulcer, psychoneurosis, colitis, late lues and intermittent hyperbilirubinemia. In all, there are 11 negative cases.

The cases shown to be positive on cultivation were 2 cases of pernicious anemia. In both these cases there were *B. coli*. Also in 2 cases of chronic cholecystitis there were *B. coli*. In one case of cholelithiasis there was growth of streptococcus faecalis in bile from the gall-bladder (after  $\text{MgSO}_4$ ). In a case of gastroenteritis there was streptococcus faecalis, and in a case with achylia after subtotal gastrectomy there was staphylococcus pyogenes.

#### SUMMARY

These preliminary investigations have shown that the duodenal juice is generally sterile. In cases of achlorhydria there are coli, streptococci and staphylococci in the duodenal juice and bile. In two cases of cholecystitis there was a coliflora. In one case of cholelithiasis there was streptococcus faecalis in the gall-bladder bile. In a case of gastroenteritis there was streptococcus faecalis +  $\beta$ -hemolytic streptococci.

The consistently negative cultivations, with the exception of cases with clear pathological changes in the digestive tract, seem to indicate that this technique satisfies reasonable bacteriological requirements for the suction of duodenal juice and bile for cultivation. Such cultivations may in the future prove to be of increased importance for the examination of the flora in the upper part of the duodenum and in the bile ducts and gall-bladder.

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## OBSERVATIONS ON THE SECRETION OF ACID BY THE MOUSE STOMACH IN VITRO

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### INTRODUCTION

Our previous papers (Davenport 1947, Davenport and Jensen 1948) have described some aspects of the oxidative metabolism of the mouse stomach and the conditions under which acid secretion occurs in vitro. The present report contains additional observations on the pharmacology of secretion in vitro and on the nitrogen and pyruvic acid metabolism of the stomach as related to the acid secretion.

### METHODS

The methods of preparing the excised stomach and incubating it in salt solution were the same as previously described (Davenport and Jensen 1948) with two important changes. In the present series of observations the stomach when filled with fluid was placed in a 50 x 25 mm. weighing bottle instead of in a Warburg flask. The bottle contained 2 ml. of the salt solution and was fitted with a rubber stopper through which passed glass tubes for aeration. The stomach was completely covered by the external fluid.

Instead of using white mice obtained from dealers we used an inbred strain (CBA, Strong) raised in this laboratory. The mice were used when they were about 60 days old, long before the spontaneous mammary tumors to which this strain is susceptible would appear. The stomachs of these mice were smaller, thinner and more uniform than those of the white mice previously used. The dry weights of the secreting portion of the stomachs averaged 20 mg.

The inorganic acid presumed to be secreted by the stomach was calculated by subtracting from the total acid found by titration the observed lactic acid and the calculated carbonic acid. The factor used to calculate the carbonic acid present, as determined in independent analysis of the internal fluid, was 0.24 micromoles per ml. per mg. dry weight.

The salt solution was that previously described (Davenport 1947), and glucose was always present in 0.02 M concentration.

### CONTROL OBSERVATIONS

Usually one group of experiments each week was devoted to control observations in which only glucose was added to the salt solution. Our hope that the control observations on the inbred mice would yield more uniform

results than those obtained on white mice was disappointed. The results of 72 control observations are shown in Fig. 1 where the amount of acid secreted is plotted against the dry weight of the secreting part of the stomach.

There is a correlation of  $+0.46$  between the two variables. However, it is obvious that the scatter of the points is so great that it is difficult to use the data for comparison with other data obtained under different experimental conditions. It was observed that if the data obtained on stomachs weighing more than 24.9 mg. were excluded there was zero correlation between the variables. The mean values of acid secretion in the three weight groups below 25 mg. are drawn as horizontal lines in Fig. 1. It can be seen that these values are nearly identical. The mean value of the acid secretion

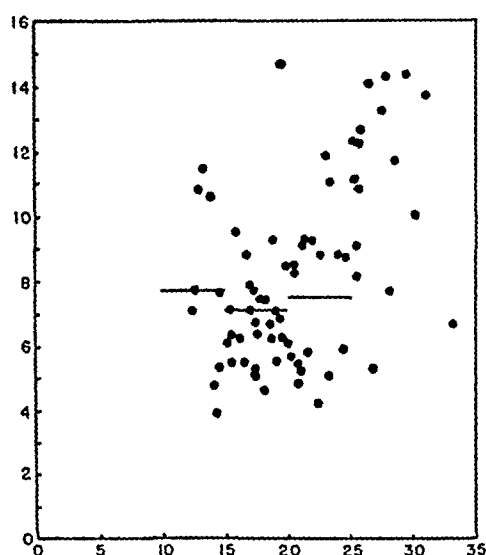


FIG. 1. ORDINATES: MICROMOLES OF ACID SECRETED PER 120 MIN.; ABSCISSAE: DRY WEIGHT OF SECRETING PART OF STOMACH IN MILLIGRAMS

and standard error of the mean in the 59 observations on stomachs weighing less than 25 mg. was found to be  $7.67 \pm 0.21$  micromoles per 120 mm. All other experimental results, after observations made on stomachs found to weigh more than 24.9 mg. were excluded, were compared with this value.

#### CARBONIC ANHYDRASE

Because the control data were so variable an attempt was made to correlate the acid secretion with the amount of carbonic anhydrase in the mucosa. Most of the enzyme in the mucosa is confined to the parietal cells (Davenport 1939, 1940), and the total amount of the enzyme in the mucosa is a measure of the number of parietal cells present. This latter quantity should in turn be related to the amount of acid secreted.

The acid secretion was measured in the usual way, but the stomach in-



stead of being dried was ground in a glass homogenizer and analysed for carbonic anhydrase by the method of Meldrum and Roughton (1933). The results were expressed in the same units (E) as used in all previous work by Davenport (1939 et seq.). The results are given in Fig. 2.

In Fig. 2a the total enzyme units are plotted against the wet weight of the secreting part of the stomach. There is an excellent correlation of  $+0.80$  between the variables. This is evidence contradicting our previous supposition (Davenport and Jensen 1948) that the number of parietal cells might decrease as the size of the stomach increases. In Fig. 2b the acid secreted is plotted against the total enzyme units. The correlation is only  $+0.35$ .

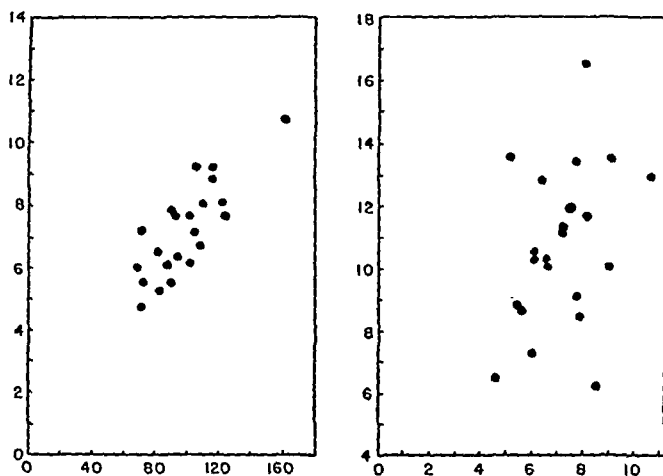


FIG. 2a, left. Ordinates: carbonic anhydrase in stomach in hundreds of units; abscissae: wet weight of secreting part of stomach in milligrams.

FIG. 2b, right. Ordinates: acid secreted in micromoles per 120 min.; abscissae, carbonic anhydrase in hundreds of units.

It is obvious that these results afford no better basis for control observations than do the simpler determination of dry weight.

#### PHARMACOLOGICAL OBSERVATIONS

Carbaminoylcholine was added to the salt solution in concentrations ranging from 0.00001 to 1 mg.  $\%$ . No effect on acid secretion was observed. This is in contrast to our previous results in which the drug was found to increase acid secretion. A possible explanation for the negative results obtained is that the stomachs were secreting at the maximum rate possible under the conditions of the experiment and were not susceptible to further stimulation. A source of stimulation not present in the earlier experiments was distention of the stomach. When the Warburg flasks were used it was not possible to inflate the stomachs fully and still get them through the mouth of the flasks. When weighing bottles were used we distended the

stomachs to their maximum size before placing them in the bottles for incubation. Distention of the intact stomach does stimulate acid secretion, probably through a humoral mechanism (Grossman, Robertson and Ivy 1948), and it is possible that a similar mechanism is present in vitro.

Atropine sulfate was added to the salt solution in concentrations ranging from 0.00001 to 1 mg.  $\%$ . The results are shown in Fig. 3 where the acid secretion as per cent of the control rate is plotted against the log of the drug concentration. Each point represents the mean of at least eight observations. It can be seen that atropine inhibits secretion in vitro. It is not known whether atropine directly inhibits the secretory mechanism or inter-

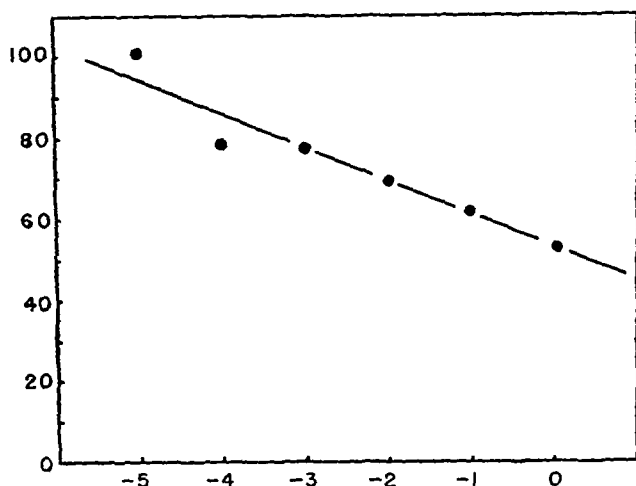


FIG. 3. ORDINATES: RATE OF ACID SECRETION IN PER CENT OF CONTROL; ABSCISSAE: CONCENTRATION OF ATROPINE SULFATE IN LOGARITHMS OF MILLIGRAMS PER CENT

feres with whatever stimulatory mechanisms are operating in the excised stomach.

Ethyl alcohol (50 mg.  $\%$ ) and Difco Bactopeptone (100 mg.  $\%$ ) were found to have no effect on the acid secretion.

#### NITROGEN METABOLISM

Some aspects of the nitrogen metabolism of the stomach were investigated in a series of experiments in which representative amino acids were added to the salt solution. In addition to the usual analyses the internal fluid was also analysed for ammonia at the end of the incubation period. No ammonia was found when the amino acids were absent. No ammonia was found when the following amino acids were present in concentration of 25 mM/l: DL-serine, D-glutamic acid and DL-aspartic acid. Small amounts of ammonia (maximum 0.97 micromoles) were found when glycine, DL-alanine and DL-arginine were present. The deaminating system of the

stomach is not very active. The amino acids had no effect upon acid secretion.

Glick (1948) has shown that urease is present in the stomach. The enzyme distribution is associated with that of the parietal cells, and the concentration of the enzyme appears to vary directly with the ability of the stomach to secrete acid. Urease is an enzyme which converts a substrate having no ionic charges into end products which are ions. It is possible to conceive of a scheme of acid secretion in which urease would have a part. However, in eight experiments in which urea was present in concentration of 25 mM/l the acid secretion was found to be  $7.21 \pm 0.76$  micromoles per 120 min. as compared with the control rate  $7.67 \pm 0.21$  micromoles per 120 min. In these experiments an average of 1.27 micromoles of ammonia appeared.

TABLE I

*Acid accumulation in micromoles in the mouse stomach incubated 120 min. in glucose containing salt solution*

SUPPLEMENTS	n	TOTAL ACID	CAR-BONIC ACID	LACTIC ACID	PYRUVIC ACID INSIDE	PYRUVIC ACID OUTSIDE	
	59	$9.86 \pm 0.44^*$	0.50	$1.69 \pm 0.74$	—	—	$7.67 \pm 0.21$
0.34m M arsenite	8	$8.68 \pm 0.56$	0.58	$0.94 \pm 0.70$	$0.00 \pm 0.03$	—	$7.26 \pm 0.53$
0.02 M acetate	15	$7.60 \pm 0.06$	0.48	$1.64 \pm 0.14$	$0.24 \pm 0.06$	$0.32 \pm 0.06$	$5.24 \pm 0.15$
0.34m M arsenite	7	$7.65 \pm 0.29$	0.40	$1.58 \pm 0.16$	$0.22 \pm 0.09$	—	$5.45 \pm 0.14$

\*Standard error of the mean.

These results make it appear unlikely that urease is a part of the secretory mechanism. In addition we have obtained acid secretion in more than 1000 experiments on the excised stomach in which no urea whatever was added. Consequently it can be concluded, until strong positive evidence is forthcoming, that urease is not an essential part of the secretory mechanism.

The addition of ammonium chloride in a concentration of 25 mM/l did not increase acid secretion, thereby providing experimental evidence against the old theory of Mathews (1920) implicating ammonium chloride in acid secretion.

#### PYRUVIC ACID METABOLISM

We have shown (Davenport 1947) that although negligible amounts of pyruvic acid accumulate when the stomach is incubated in vitro the stomach is capable of forming pyruvic acid, oxidizing it and reducing it to lactic acid. Since Bull and Gray (1945) have suggested that pyruvic acid is the source of hydrogen ions occurring in the acid secretion we have studied the metabo-

lism of pyruvic acid as related to acid secretion with the results shown in Tables I and II.

The first line of Table I shows the control observations in which the acid secreted was calculated on the assumption that pyruvic acid was absent from the internal fluid. The second line gives the results obtained in experiments in which pyruvic acid was measured by the enzymatic decarboxylation of pyruvate. They show that the acid is absent. The third line shows that 0.34 mM arsenite, an inhibitor of pyruvic acid oxidation (Peters, Sinclair and Thompson 1946), inhibits acid secretion and allows the accumulation of pyruvic acid. The acid secretion is inhibited by about 2 micromoles, but only 0.56 micromoles of pyruvic acid accumulate. The last line shows that acetate does not reverse the inhibition of acid secretion produced by arsenite.

TABLE II

*Pyruvate utilization in micromoles per 120 min. in the presence of 5 mM pyruvate*

	INHIBITION OF ACID SECRETION	n	PYRUVATE DISAPPEARING	LACTATE APPEARING
	%			
Controls.....	0	8	$2.01 \pm 0.36$	$1.73 \pm 0.24$
30 mg. % SCN <sup>-</sup> .....	38	8	$2.04 \pm 0.18$	$1.79 \pm 0.21$
0.34 mM arsenite.....	30	8	$0.65 \pm 0.17$	$1.08 \pm 0.17$

The first line of Table II shows that 2 micromoles of pyruvic acid disappear in 120 min. As pyruvic acid disappears lactic acid accumulates. A part of the lactic acid appearing comes from endogenous sources, for the pyruvic acid present prevents the oxidation of lactic acid (Green and Brosteaux 1936). The rest comes from the reduction of pyruvic acid. The results in the second line show that although thiocyanate ions inhibit acid secretion more profoundly than does arsenite, they have no effect on pyruvic acid utilization. The results in the last line show that 0.34 mM arsenite produces about 60% inhibition of pyruvic acid utilization while reducing acid secretion 30%.

These results demonstrate that there cannot be a mole for mole relation between pyruvic acid metabolism and acid secretion. One molecule of pyruvic acid cannot provide one hydrogen ion for the secretion. The alternative possibility that one molecule of pyruvic acid gives rise to four hydrogen ions is unlikely for many reasons. Arsenite is not a specific inhibitor of pyruvic acid oxidation, and its effect on acid secretion is probably the result of its inhibition of other enzymes.

Thiamine is essential for the reactions involved in pyruvate oxidation in mammalian tissues. Shay, Komarov, Gruenstein and Fels (1946) have shown that the rate of acid secretion is not reduced below normal in severely thiamine-

deficient rats. Although Shay et al. did not demonstrate that pyruvate metabolism was in fact interrupted in their rats, their experiments strongly support our tentative conclusion that pyruvic acid metabolism is probably not associated with acid secretion.

Some pyruvate oxidized in tissues is oxidized to acetate. It is conceivable that acetate, perhaps, in the formation and hydrolysis of acetyl phosphate, is concerned in acid secretion, but the addition of acetate does not reverse the arsenite inhibition.

#### SUMMARY

Further observations have been made on the secretion of acid by the mouse stomach in vitro. The rate of acid secretion was found to be poorly correlated with the dry weight of the stomach or the amount of carbonic anhydrase present.

Carbaminoylcholine was found not to stimulate acid secretion in this series of experiments. Atropine inhibited secretion. Ethyl alcohol and pepsin had no effect.

The stomach was found not to contain a conspicuously active system for deaminating amino acids.

The addition of urea did not increase acid secretion, and it is concluded that urease is probably not an essential part of the acid secreting mechanism.

Observations on the formation and utilization of pyruvic acid by the stomach showed that there is not a 1:1 relation between pyruvic acid appearance or disappearance and acid secretion. It is concluded that pyruvic acid metabolism is probably not an essential part of the acid secreting mechanism.

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## PRODUCTION OF ULCERATIVE COLITIS IN DOGS BY THE PROLONGED ADMINISTRATION OF MECHOLYL\*

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### INTRODUCTION

The daily administration of mecholyl to dogs produces a bloody diarrhea which closely resembles that seen in human acute ulcerative colitis, and at autopsy the outstanding feature is the hemorrhagic appearance of the gastrointestinal tract. With the prolonged daily administrations of this drug a sequence of pathological changes, ranging from mucosal hemorrhages through erosions to acute and subacute ulcerations can be produced. The lesions found in the stomach and duodenum have already been described<sup>1</sup>. The pathological changes which are produced in the large intestine of these animals is the subject of this report.

### METHOD

The details of the methods employed in these experiments have already been described<sup>1, 2</sup>, and consist essentially of the daily prolonged administration of subcutaneous injections of mecholyl in aqueous solution in one group of dogs, and the daily intramuscular injections of mecholyl embedded in a beeswax-mineral oil mixture in another group of animals (Table I and II).

### RESULTS

#### *A. Effects of Daily Intramuscular Injections of Mecholyl Embedded in Beeswax*

The experimental data are summarized in Table I. Following the injections of mecholyl a sequence of pathological changes occurred in the large bowel which consisted of marked hyperemia and engorgement of the blood vessels, interstitial mucosal hemorrhages with superficial necrosis, erosions, focal areas of acute colitis and acute or subacute ulcerations. The dogs had received from 2 to 71 injections over a period of 2 to 73 days. Erosions, acute focal colitis or ulcerations were encountered in 4 of the 19 dogs injected (Table I).

The generalized parasympathetic responses which accompanied every injection of mecholyl have already been described<sup>1</sup>. Although the quantities of mecholyl injected with the beeswax mixture were greater than the subcutaneous

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lethal dose for these dogs, the general responses were not as severe as when mecholyl alone was given subcutaneously, but the effects were more prolonged<sup>1, 2</sup>.

The outstanding feature of these experiments was the marked bloody diarrhea which came on soon after almost every injection of mecholyl. The stools were well formed at first and of normal color and consistency, but within

TABLE I  
*Effects of the prolonged administration of mecholyl in beeswax-mineral oil mixture*

EXP. NO.	DOG NO.	WT.	DAILY DOSE	NO. OF DOSES	TIME	RESULTS: COLON	REMARKS
		kg.	mg.				
1	41	14.5	80- 90	3	3	Hyperemia	Died 10 min. after last dose
2	42	8.5	25- 60	5	13	Hyperemia	Died during night from G-I bleeding
3	35	8.5	35- 80	10	17	Hyperemia	Died during night from G-I bleeding
4	36	15.9	45-125	6	6	Hyperemia	Died during the night; gut filled with blood. Pneumonia
5	38	15	45-125	6	6	Hyperemia	Died during the night from extensive G-I bleeding
6	44	10	20	4	4	Hyperemia	Died during the night. Pneumonia
7	46	9	25- 40	12	13	Hyperemia	Died during the night from extensive G-I bleeding
8	47	8	30	10	10	No change	Died during the night. Pulmonary thrombosis
9	30	7.2	20- 25	8	10	Erosions	Died during the night
10	32	10.9	40- 70	50	50	Acute focal colitis	Died 30 min. after last dose; debilitated
11	33	10	25- 55	51	51	Acute and subacute ulcers	Died during the night
12	34	6.7	50- 70	2	2	Hyperemia	Died from massive G-I bleeding
13	22	6.7	35- 50	7	7	Hyperemia	Died from massive G-I bleeding
14	27	14	30- 50	37	37	Subacute ulcers	Died 2 hours after last dose fat necrosis in peri-duodenal fat
15	17	5.9	10- 35	71	73	Hyperemia	Died 1 hour after last dose
16	23	7	30- 90	68	74	No changes	Sacrificed
17	24	6.5	30- 70	20	20	No changes	Sacrificed
18	25	8.5	80- 90	5	5	Hyperemia	Sacrificed 1 hour after last dose. Profuse rectal bleeding
19	26	9.5	80- 90	5	5	Hyperemia	Sacrificed 1 hour after last dose. Profuse rectal bleeding

10 to 15 minutes, subsequent bowel movements were looser and blood-tinged and eventually became watery, mucoid and bloody in character similar to that commonly seen in human cases of ulcerative colitis. The vomitus was frequently blood-tinged and occasionally massive hematemesis occurred.

The bloody diarrhea disappeared in most of the dogs within 2-3 hours after the mecholyl injection and within 12 to 24 hours the stools again became formed, were of normal consistency but tarry in color. In numerous instances

TABLE II

*Effects of the prolonged administration of mecholyl in aqueous solution*

EXP. NO.	DOG NO.	WT.	DAILY DOSE MECHOLYL	NO. OF DOSES	TIME	RESULTS: COLON	REMARKS
		kg.	mg.		days		
1	27	10	20-40	4	4	Hyperemia	Died 30 min. after last dose
2	45	15	40	5	7	Hyperemia	Died 1 hr. after last dose. Shock
3	28	9.1	10-15*	2	2	Mucosal hemorrhages	Died 30 min. after last dose. Shock
4	17	7.8	10-12*	2	2	Mucosal hemorrhages	Died 30 min. after last dose. Shock
5	15	19	20*	2	2	Hyperemia	Died 30 min. after last dose. Shock
6	3	20	10-15	3	5	Mucosal hemorrhages	Died 2 hrs. after last injection. Bronchopneumonia
7	21	17	10*	2	2	Severe hyperemia	Died 20 min. after last dose. G-I tract filled with blood
8	16	15	10	3	5	Mucosal hemorrhages	Died in 30 min. after last dose
9	46	17.5	10	8	10	Slight hyperemia	Died during night
10	31	17	30-40	30	40	Slight hyperemia	Healed non-specific pancreatitis with adhesions to liver
11	37	8.6	20-30	32	44	Focal acute colitis	Stomach and intestines contained bloody fluid
12	44	15.2	30-35	17	23	Focal acute colitis	Died 7 hrs. after last dose from massive G-I hemorrhage
13	35	8.1	40	6	8	Hyperemia	Died from extensive G-I hemorrhage
14	29	18.1	10-20	28	38	Hyperemia	Peri-pancreatic and peri-gastric fat necrosis
15	10	16.1	15-20	31	41	No changes	Died from infection
16	11	15	15-20	26	34	Hyperemia	Died in 30 min. after last dose. Shock
17	33	16.8	35	4	4	No changes	Died during the night. Bronchopneumonia
18	34	20	20-30	11	12	No changes	Died during the night. Bronchopneumonia
19	52	15.9	30-40	12	13	No changes	Died during the night. Bronchopneumonia
20	6	14.2	20-35	41	49	Hyperemia	Died 7 hrs. after the last dose from severe rectal bleeding
21	7	13	15-20	52	68	Hyperemia	Died from extensive G-I bleeding
22	8	14	15-25	72	86	No change	Died during the night; bilateral-adrenal hemorrhage
23	39	15	20-30	82	96	Erosions	Died 20 min. after the last dose. Debilitated
24	50	7.7	5-10	15	10	No change	Bronchopneumonia
25	49	7.7	10-15	5	5	Focal ulcerative colitis	Died during the night
26	53	18	20-40	96	104	Hyperemia	Died during the night; hemorrhage into the adrenals
27	45	16.8	15-30	111	120	Hyperemia	Peri-duodenal fat necrosis. Died from extensive G-I bleeding
28	51	20	20-30*	114	154	No change	Sacrificed: debilitated
29	13	23.5	30-50*	134	194	Acute hemorrhagic colitis	Died of extensive G-I bleeding. No malnutrition

\* Received 0.25-0.5 mg. prostigmine.



the bloody diarrhea persisted much longer, (12 to 18 hours after the injection) and many of these animals died from extensive hemorrhage into the gastrointestinal tract (Table I—Exp. 2, 3, 4, 5, 7, 12, 13). At autopsy the intes-

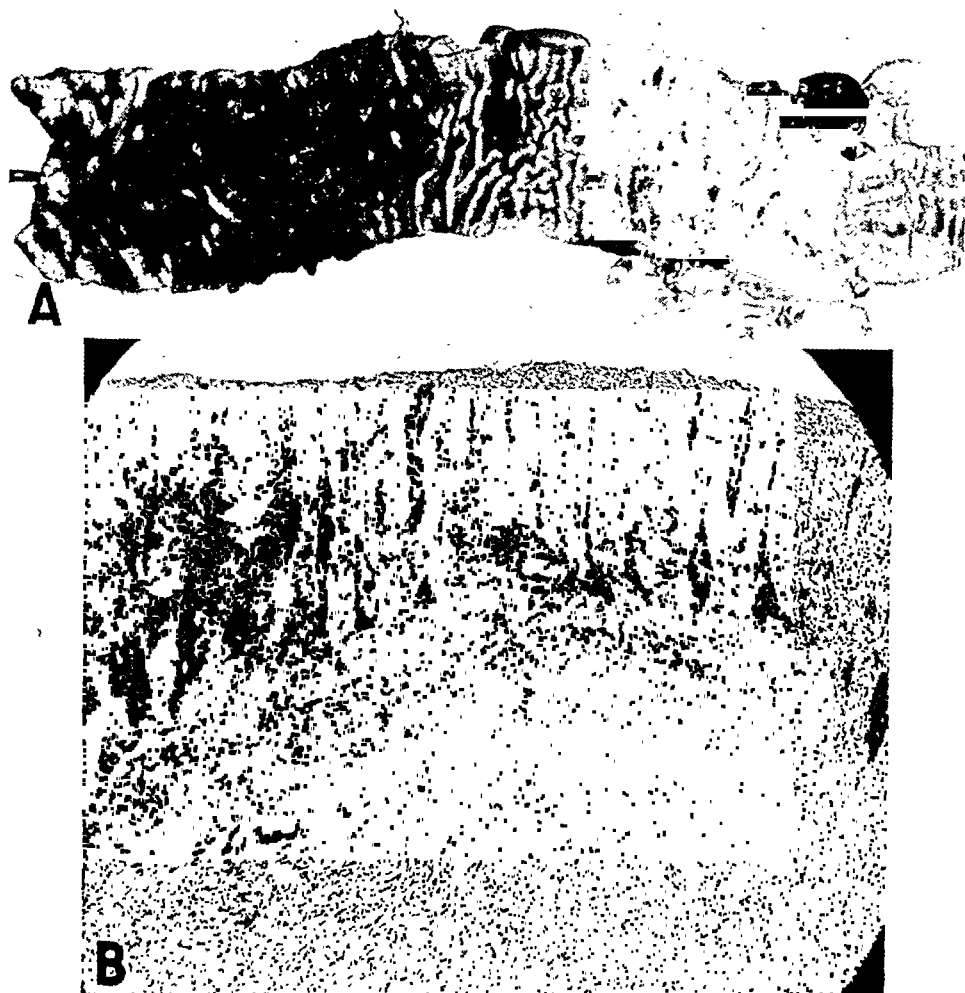


FIG. 1A. Colon, showing severe extensive hyperemia and interstitial hemorrhage.

FIG. 1B. Microphotograph of portion of above colon showing extensive interstitial hemorrhage and necrosis of the mucosa with underlying acute exudative inflammation in the submucosa. Note that the polymorphonuclear infiltration extends through the muscularis mucosa into the edematous submucosa.  $\times 90$ .

tines contained varying amounts of bright red blood, especially in the large bowel.

The mucosa of the large intestine was usually diffusely hemorrhagic with multiple mucosal interstitial hemorrhages and focal areas of superficial necrosis (Fig. 1A and B). The hemorrhagic appearance of the mucosa was more extensive and more severe than in the group of dogs which received mecholyl alone subcutaneously.

The degree of hemorrhage and superficial necrosis observed at autopsy were

mainly dependent on the time of death of the animal after the last dose of mecholyl. As in the case of the stomach and small intestines<sup>1</sup> the mucosal alterations were most pronounced within the first 3 hours after the last dose of mecholyl. In those animals which died 12 to 24 hours after the last injection from the general effects of the drug other than intestinal hemorrhage, only slight hyperemia or no changes were seen in the color. The hemorrhagic changes were generally more pronounced at the proximal and distal portions of the large intestine.



FIG. 2. ACUTE EXUDATIVE FOCAL COLITIS

Note that the entire mucosa is infiltrated by inflammatory cells. Although there is necrosis of the outer half of the mucous membrane, true ulceration has not yet occurred.  $\times 128$ .

Histological examination of the hemorrhagic portions of the colon showed the presence of interstitial hemorrhages into the mucous membranes with necrosis of the most superficial layers of the mucosa. The blood vessels were generally markedly hyperemic. In several instances the extensive hemorrhage and necrosis of the mucosa was accompanied by an acute polymorphonuclear infiltration which extended down to the submucosa, indicating the presence of a focal hemorrhagic colitis (Fig. 1B).

Multiple sections taken through the erosions seen in the gross revealed varying degrees of hemorrhage and necrosis of the mucous membrane but the basal layers were intact. In dog # 32 (Exp. 10 Table I), the necrotic tissue was not hemorrhagic, but was infiltrated by inflammatory cells, suggesting the presence of acute exudative colitis (Fig. 2).

In the two animals in which genuine ulcers of the large bowel were present, the ulcers were fairly large, irregular in contour, contained hemorrhagic bases

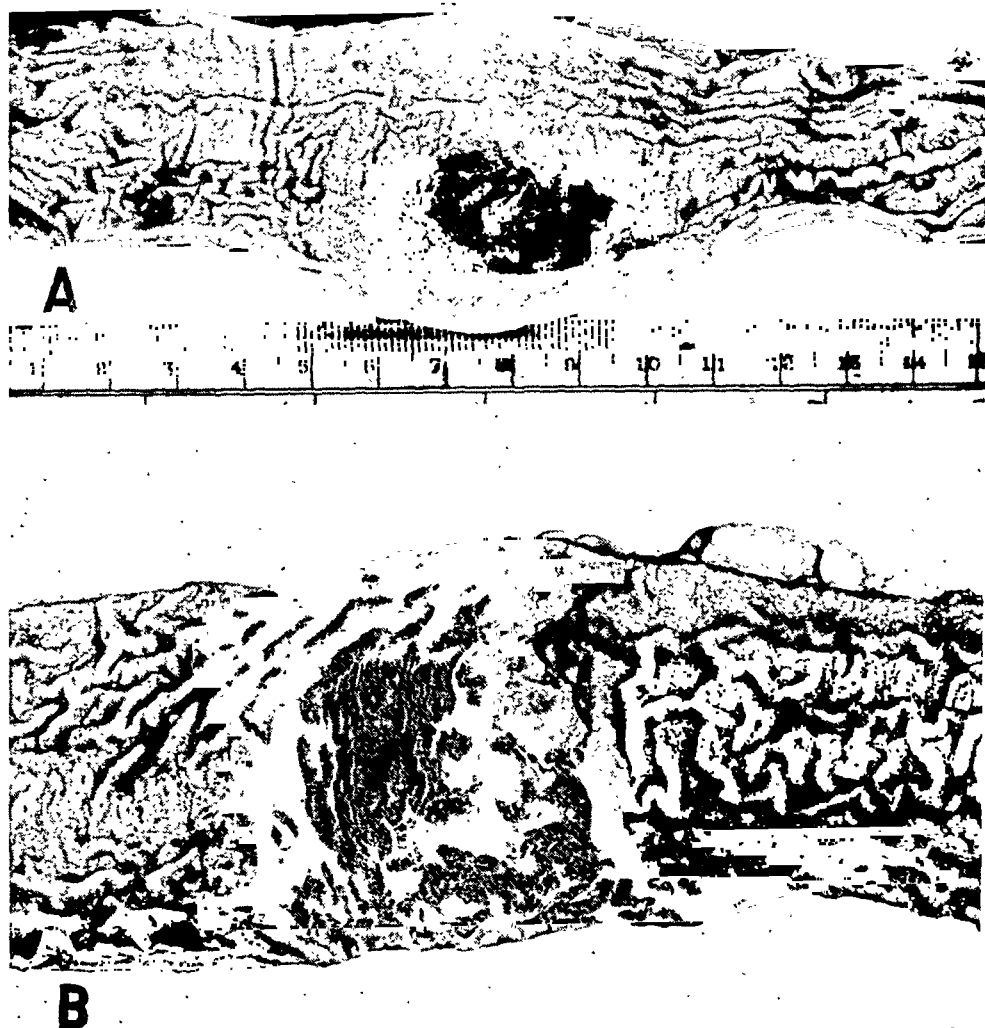


FIG. 3A (upper). Large irregular acute ulcerated area of colon in dog #33 (Exp. 11, Table I). Note the hemorrhagic base and slightly overhanging edges.

FIG. 3B (lower). Subacute ulceration in colon of dog #27 (Exp. 14, Table I).

and slightly overhanging edges. These ulcers occurred in the distal third of the large bowel (Fig. 3A and B).

In dog 33 (Exp. 11, Table I) two large ulcerated areas similar to those described above were encountered. The larger ulcer was found at the junction of the distal and middle thirds of the colon and was approximately 3.0 cm x 2

cms in size (Fig. 3A). The other ulcer measured approximately 2 x 1 cms and was close to the distal portion of the large bowel.



FIG. 4A (upper). Low power of large acute ulcer of colon seen in Fig. 3A. Note that the base is covered with necrotic debris and that the diffuse infiltration of inflammatory cells has extended into the submucosa and muscularis. The ulcer has penetrated to the muscularis.  $\times 7\frac{1}{2}$ .

FIG. 4B (lower) Higher power of large ulcer seen above, showing the extensive involvement by the inflammatory process and the degenerative changes in the muscle wall.  $\times 121$ .

Histological examination of the proximal lesion showed a large shallow ulcer, the base of which was covered with necrotic debris (Fig. 4A). The ulcer penetrated into the submucosa which was diffusely infiltrated by large numbers of polymorphonuclear leucocytes (Fig. 4B). The muscularis underlying the central portion of the ulcer revealed slight interstitial hemorrhage and degener-

ative changes in the muscle wall with relatively few infiltrating inflammatory cells. The blood vessels throughout were hyperemic and no occluded or thrombosed vessels were noted.

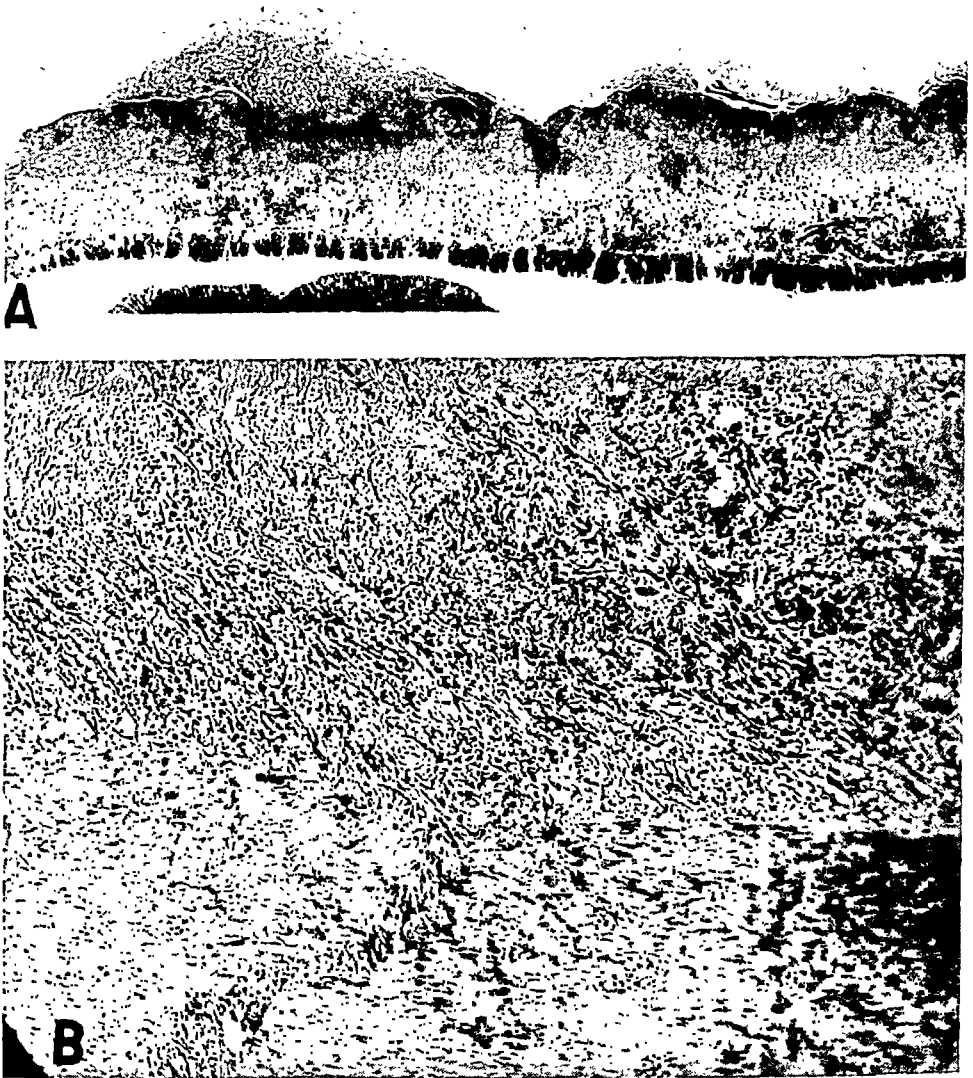


FIG. 5A (upper). Low power of large penetrating subacute ulcers of colon seen in Fig. 3B. Note the necrotic debris and the diffuse infiltration of inflammatory cells at the base of the ulcer. The inflammatory process has extended into the deeper layers.  $\times 6\frac{1}{2}$ .

FIG. 5B (lower). High power view of the base of the large subacute ulcer of colon seen above. The inflammation exudate occupies the entire submucosa and extends into the muscularis along the course of the penetrating blood vessels. Note the newly formed blood vessels and proliferating fibroblasts.  $\times 110$ .

Sections of the more distal lesion revealed essentially the same changes, but here occasionally newly formed blood vessels and a few proliferating fibroblasts were noted at the edges of the ulcer. The underlying muscularis did not show degenerative changes and no evidence of re-epithelialization

could be seen. Both ulcers appeared to be of an acute nature, but the proliferation of fibroblasts in the more distal lesion suggested that it may have been of slightly longer duration than the proximal ulcer.

In the other dog (Exp. 14, Table I), the ulcer was somewhat larger than those seen in dog 33 (Fig. 3B). Microscopically this lesion was essentially similar to those described above, but appeared to be somewhat older as indicated by the presence of a great increase in the number of newly formed blood vessels, and proliferating fibroblasts. The inflammatory exudate extended into the muscle layers.

This lesion was regarded as being of a subacute nature. No distinct vascular lesions or vascular thrombosis were present. The blood vessels were generally hyperemic (Fig. 5A and B).

#### *B. The Effects of Daily Repeated Subcutaneous Injections of Mecholyl (Aqueous)*

The experimental data are summarized in Table II. The pathological changes in the large bowel were less pronounced and were of shorter duration than in the dogs which had received the injections of mecholyl in beeswax. The animals received 10 to 50 mgm. of mecholyl daily over a period from 2 to 101 days, having received a total of 2 to 134 injections. No ulcers were found in this group studied, although areas of focal colitis or erosions were encountered in 5 of the 29 dogs injected.

The generalized parasympathetic effects which accompanied every injection of mecholyl have been described elsewhere<sup>1</sup>.

The character of the vomitus and the stools was similar to that observed after the mecholyl in beeswax injections. The hemorrhagic appearance of the colon was not as extensive or as severe as in the dogs which received the mecholyl in beeswax. The microscopic changes were essentially similar, although no true ulcers were encountered in this group of animals.

#### DISCUSSION

The results of this study demonstrate that the prolonged daily administration of mecholyl may produce a series of pathological changes in the large bowel ranging from severe hyperemia, interstitial mucosal hemorrhages, through erosion to true ulcer formation. The outstanding features of these experiments were the bloody diarrhea noted after almost every injection of mecholyl and the hemorrhagic appearance of the gut at autopsy (Fig. 1).

Microscopic examination of the numerous sections taken from the large bowel of these animals strongly suggests that the vasodilatory action of mecholyl on the blood vessels was the main factor in the pathogenesis of these lesions, and the sequence of pathological events was probably as follows: The marked vascular hyperemia and engorgement gave rise to stasis, increased capillary permeability and tissue anoxemia, which resulted in extravasations of red

blood cells into the mucosa which was followed by superficial necrosis of the mucous membrane, erosions, and finally led to the formation of true ulcers. This pathological process was similar to that which resulted in the formation of gastric and duodenal ulcers after the administration of mecholyl<sup>1</sup>.

Lium<sup>3</sup> has stressed the importance of increased contractions or spasm of the musculature of the colon in the production of large bowel lesions. In our experiments, the trauma resulting from the vigorous contractions of the large bowel after mecholyl upon an engorged friable mucous membrane may have been an additional factor in the production of the pathological changes encountered.

It has been shown that the vasomotor state of the colonic mucosa in dogs<sup>4</sup> and in man<sup>5</sup> may be altered by emotional disturbances. Stimulation of the sympathetic nerves to the colon resulted in blanching, whereas blushing of the mucosa was produced by stimulation of the parasympathetic nerves<sup>6</sup>.

It has also been demonstrated that continuous vagal stimulation in dogs produces a diarrhea, which is occasionally blood-tinged or tarry in color and at autopsy the mucosa of the gastrointestinal tract including the large bowel are found to be hyperemic and hemorrhagic<sup>7</sup>. Hyperemia and hemorrhage of the colon have also been observed following experimental lesions in the brain stem of dogs<sup>8</sup>. Gross changes of the mucosa of the large intestine, including some changes in the stomach and small intestine have been observed at autopsy in patients who died from shock post-operatively<sup>9</sup> and in animals in which experimental shock was produced by intraperitoneal injection of adrenalin<sup>10</sup>. These authors suggested that initial vasospasm and associated vasomotor changes which occur in shock were responsible for these lesions.

In a recent review of the neuro-humoral aspects of peptic ulcer formation, the significance of marked circulatory disturbances in the initiation of acute gastric or duodenal lesions were re-emphasized<sup>11</sup>. The results of this present study has demonstrated the importance of repeated profound vascular disturbances as a main factor in the production of acute ulcerative lesions in the large bowel of dogs.

It is therefore suggested that sustained emotional conflicts which are known to be associated with the onset and relapses of ulcerative colitis in man<sup>12, 13, 14</sup> may create an imbalance of the autonomic innervation of the large bowel resulting in alterations of the vasomotor state of the blood vessels.

If these vascular alterations be prolonged or severe enough they may produce mucosal lesions which in some cases go on to true ulceration.

#### CONCLUSIONS

(1) Severe hyperemia, mucosal hemorrhages, erosions and acute and sub-acute ulcerative colitis has been produced in dogs by the prolonged daily administration of mecholyl.

(2) Hyperemia, vascular stasis, altered capillary permeability, interstitial mucosal hemorrhages, tissue anoxia and necrosis of the mucosa, erosions and true ulcer formation are suggested as the probable sequence of events in the pathogenesis of these lesions. The additional factor of trauma has been discussed.

(3) A vascular concept of the initiation of ulcerative colitis is suggested.

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## EXPERIMENTAL EVALUATION OF A NEW GASTROINTESTINAL ANTISEPTIC—SODIUM PHTHALYLSULFACETIMIDE\*

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It has been demonstrated that N<sup>4</sup> acyl derivatives of sulfonamide compounds are sparingly absorbed from the gastrointestinal tract and that many of these agents possess good antibacterial action in vivo<sup>1-9</sup>. While examining several new compounds belonging to this general group, in continued search for an ideal intestinal antiseptic, one product seemed of particular interest. This drug, sodium phthalylsulfacetimide or disodium N<sup>1</sup>-acetyl-N<sup>4</sup>-phthalyl-sulfanilamide dihydrate (Fig. 1), demonstrated, in preliminary test, good bacteriostatic activity against coliform organisms in vitro as well as in human beings. In addition, it showed satisfactory activity in vitro against many bacterial pathogens of the gastrointestinal tract, especially the *Shigella* group<sup>10</sup>.

The main value of nonabsorbable sulfonamides in the treatment of gastrointestinal infections appears to lie in the possibility of obtaining and maintaining excessive sulfonamide concentrations inside the lumen of the small and particularly the large intestines without the production of appreciable tissue concentrations anywhere else in the body, a situation which cannot be achieved with absorbable products. However, the phenomenon of non-absorbability of N<sup>4</sup> acylated products appears to be valid only in the presence of an intact intestinal mucosa, since extensive absorption takes place from serous cavities and wound surfaces<sup>3-5, 11</sup>. On the other hand, it has been claimed that non-absorbable sulfonamides exert only a *surface* action which should limit the usefulness in deep seated infections, whereas absorbable compounds are carried to the gut wall by way of the blood stream and thus have a better chance of reaching the deeper tissue layers.

The present report deals with the toxicity of sodium phthalylsulfacetimide and its fate in the body after administration by various routes. In addition, it contains data from experiments which were expected to throw some light on the problem of penetration of N<sup>4</sup> acylated sulfonamides into the various layers of the intestinal wall.

Following is a list of all studies which comprise the present investigation:

1. Some physico-chemical properties of sodium phthalylsulfacetimide
2. Acute, subacute and chronic toxicity in albino rats
3. Absorption and excretion after oral, subcutaneous, intraperitoneal and

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intravenous administration in rats and rabbits and after oral administration in man

4. Behavior of a nonabsorbable and absorbable sulfonamide in the gastrointestinal tract
  - a. concentration of dissolved drug in the contents of the stomach, and small and large bowel, after oral administration in rabbits
  - b. penetration of drug into the intestinal wall of the rabbit
  - c. diffusion of drug through isolated surviving loops of jejunum of the rat.

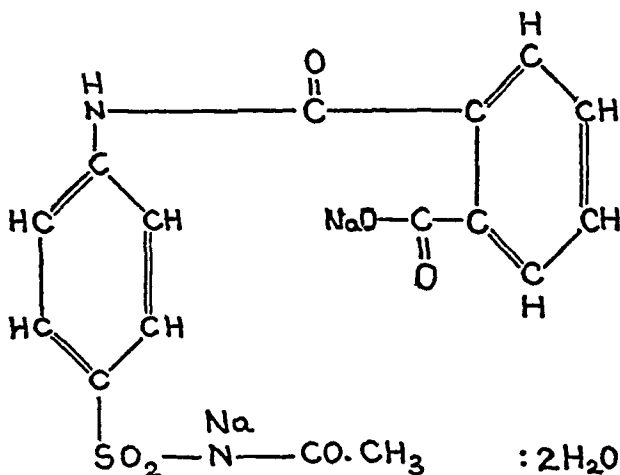


FIG. 1

## MATERIALS AND METHODS

### 1. Toxicity

Young albino rats from our own standard strain of uniform age and weight (160–200 grams) were used in all toxicity studies. The animals were raised on a standard diet (Rockland Farms rat diet), and had free access to water.

For determination of the oral and intraperitoneal acute toxicity the rats were observed over a period of four days following the administration of the drug. At least 10 animals were used for each dose level, not counting smaller preliminary test groups at both ends of the toxicity curves. Post mortem examinations were performed on all animals.

For intraperitoneal injection, 20 per cent aqueous solutions of the sodium salts were used. The sulfonamide concentration in the blood was determined from the tail vein of each animal, at least on one occasion, in order to eliminate rats injected inadvertently into the gut instead of intraperitoneally. Phthalylsulfacetimide was administered as a 20% suspension in 10% gum acacia.

The subacute toxicity was determined by daily intubation of 20% sodium phthalylsulfacetimide for a period of 5 days.

The chronic toxicity was determined by incorporating the drug in 5 and 10%

concentrations into the powdered form of the standard diet. The experiments were conducted with weanling rats weighing about 90 grams and planned for a period of six weeks. The food consumption was checked daily. The body weight of each animal was recorded twice weekly. Blood concentration and total urinary elimination of sulfonamide were determined at the same intervals. For the purpose of urine collection, subgroups consisting of 5 animals each were placed into separate metabolism cages. The nonprotein nitrogen levels in the blood were estimated upon termination of each experiment. Complete blood counts were performed at the start and six weeks later at the close of the study.

In all experiments the surviving rats were killed by exsanguination under ether anesthesia. Post mortem examinations were performed on these animals and also, whenever feasible, on rats succumbing during an experiment. The most important organs of representative animals were fixed in formaldehyde for histological study.

## *2. Absorption-excretion*

In rats, subgroups of 5 animals, kept without food for 17 hours prior to the start of the test, were placed in metabolism cages. The drugs were given by stomach tube, subcutaneously, and by intraperitoneal injection. Blood samples were taken from the tail vein at predetermined intervals and the total urinary output was collected for estimation of the sulfonamide concentration. In some experiments the sulfonamide content was determined also in the stools.

In rabbits similar procedures were employed. The intravenous route was used in addition. These animals were placed in individual metabolism cages. Blood samples were obtained from the ear vein.

In human beings, sodium phthalylsulfacetimide was administered orally to fasting individuals with a measured amount of fluid. No further fluid or food was allowed for three hours following medication to insure equalized conditions of absorption and initial distribution in the small intestines. Blood samples were taken from the antecubital vein 1, 4, 8, and 24 hours after administration of the test dose and the total urinary output was collected for 48 hours.

## *3. Drug Concentration in Contents and Wall of Rabbit Gut*

For determination of the level of *dissolved* drug in the contents of the gastrointestinal tract at various heights, rabbits were killed 4 hours after receiving a test dose of the drug by stomach tube. After exposure of the gut, double ligatures were placed immediately in order to separate stomach, jejunum, ileum and large intestines. These organs were then opened sepa-

rately and the contents collected in dry beakers, first for passage through gauze and then, if possible, for filtration through no. 2 or no. 4 Whatman filter paper under suction, in an effort to obtain sufficient clear filtrate for estimation of the sulfonamide concentration. It was not possible in all instances to obtain liquid material from all parts of the gastrointestinal tract, particularly with sodium sulfadiazine that was used as our standard of an absorbable sulfonamide in these experiments. Blood levels were determined simultaneously.

In analyzing the concentration in the gut wall, rabbits were killed 3, 6, and 17 hours after receiving the test dose. Blood was collected for determination of the drug level. Loops of gut about 4–6 cm. long were excised from the stomach, jejunum, ileum and colon, opened and thoroughly rinsed with distilled water. Adjoining pieces were taken for removal of the mucous membrane and the muscularis. Detachment of the mucous membrane is simplest in the stomach where it is thick and only loosely connected to the muscularis. Separation in the rest of the gut was accomplished in all instances by stretching the strip between pins on a corkplate with the mucosa facing upward. With the help of a sharp scalpel the mucosa could then be readily scraped off. Care was taken to scrape only in one direction in order to prevent any possibility of massaging drug from the mucosa into the deeper layers of the gut. More determined scraping will remove the muscularis also, leaving only a fine transparent membrane—the serosa. Sample strips of the scraped and intact gut were cut off and fixed in 10% formaldehyde for histological examination. It was thus possible to check the success of the procedure and to verify the removal of the desired layers under the microscope. The final tissue piece slated for chemical analysis was then weighed on a torsion balance and extracted in accordance with a procedure previously described in detail<sup>12</sup>.

The diffusion of sulfonamide agents through the gut wall was studied by means of isolated loops of jejunum from rats, suspended in an oxygenated Ringer bath at 38°C. Immediately after excision from the animal, the loop was cleaned of its contents. A small glass funnel was then tied into the proximal end and the drug to be tested was introduced in form of a solution or suspension, in accurately measured quantity, or as a dry powder, through this funnel with the help of a syringe. The lower end of the loop was firmly closed with a ligature, which was used for fixation of the gut in the bath containing 100 cc. of Ringer solution. The loop was kept suspended in the Ringer solution in such a manner that the glass funnel, protruding from its proximal end, remained safely above the level of the Ringer bath and that no tension was exerted upon the gut. The loops usually displayed strong peristaltic activity immediately after suspension which continued for hours with gradually diminishing strength. The fluid level inside the funnel was seen to rise and fall with each peristaltic wave, insuring constant mixing of the gut contents.

Samples of Ringer solution were taken from the bath at predetermined intervals for estimation of the sulfonamide concentration.

The method of Bratton and Marshall<sup>13</sup> was employed in the determination of "free" sulfonamide. Concerning phthalylsulfacetimide, it was found imperative to carry out determination of free sulfacetimide with a minimum of delay after trichloroacetic acid or p-toluenesulfonic acid had been added for precipitation of the proteins and in preparation for diazotization, since in the presence of acid, phthalylsulfacetimide, like other phthalyl sulfonamides<sup>14</sup>, is fairly rapidly split at room temperature to sulfacetimide and phthalic acid. Solutions of the "free" parent compounds diazotized simultaneously with the particular sulfonamide under study served as standards for photoelectric colorimetry. "Total" sulfacetimide was determined by heating the acid filtrate of blood, tissue extracts or urine after addition of 0.25 cc. of 4N hydrochloric acid for 1 hour at 100°C.

Although the addition of hydrochloric acid was found superfluous for the splitting of phthalylsulfacetimide, it seemed indicated since "conjugated" sulfacetimide may consist also of acetylsulfacetimide. However, it should be realized that this compound could have been formed in the body only from the minimal amounts of sulfacetimide liberated from phthalylsulfacetimide at the pH of tissue fluids. It was assumed, therefore, that "conjugated" sulfacetimide is composed mainly of phthalylsulfacetimide, since, as will be demonstrated, sodium phthalylsulfacetimide is freely soluble and rather stable at the pH of tissue fluids. All results were expressed in terms of this compound by multiplying the values for "free" sulfacetimide with the factor 2.06.

## RESULTS

### *1. Some Physico-chemical Properties of Sodium Phthalylsulfacetimide*

Sodium phthalylsulfacetimide is soluble in less than 1 part of water. Low concentrations are weakly acid, higher concentrations are slightly alkaline (Table I). If the sparingly soluble phthalylsulfacetimide (56 mgm. % in water at room temperature) is introduced in powder form into buffer solution at the range of pH 5-8 (200 mg. in 100 cc.), it is easily and completely dissolved down to a pH of 7 due to the formation of sodium phthalylsulfacetimide (Table II). Spontaneous hydrolysis is negligible in the alkaline range and remains low down to a pH of about 6.0. Below pH 5.5 there occurs a sudden, rapid increase in splitting which reaches almost 50% at a pH of 4.2 within 24 hours.

It is obvious, therefore, that no significant "deconjugation" would be expected at the physiological hydrogen ion concentration of tissue fluids. On the other hand, any delay in the diazotization of acid tissue filtrates would lead

to the erroneous assumption of cleavage in the body, which actually occurred in the test tube.

## 2. Toxicity

*a. Acute Toxicity.* The results are based mainly on studies in male rats. Female animals were found to be somewhat more sensitive. The low acute toxicity of sodium phthalylsulfacetimide is illustrated in Table III. It is apparent that no death occurred from an oral dosage of 10 gram/kg. of this

TABLE I  
*pH of aqueous solutions of sodium phthalylsulfacetimide*

CONCENTRATION OF SOLUTION	pH
%	
1	6.55
5	6.76
10	7.12
20	7.30

The pH was determined with a Cambridge Electron Ray pH meter.

TABLE II  
*Solubility and spontaneous hydrolysis of phthalylsulfacetimide in buffers of varying pH after 24 hours at room temperature*

pH OF BUFFER	pH AFTER ADDITION OF 200 MG. PHTHALYLSULFACETIMIDE PER 100 CC. BUFFER	MG. % SULFONAMIDE FOUND	PER CENT SPLITTING
8.00	7.11	200	2.4
7.38	7.01	200	2.4
6.85	6.66	154	3.0
6.80	6.70	145	4.6
6.30	6.20	148	5.0
5.82	5.51	106	10.0
5.33	4.40	101	33.0
5.02	4.21	60	46.0

compound and even with amounts of 14 and 15 gram/kg. the survival rate still remained at 40%. Phthalylsulfacetimide used for comparison showed a rather similar toxicity curve, indicating that the high solubility of the sodium salt had no influence on its oral toxicity. Blood levels in all rats were negligible for phthalylsulfacetimide as well as for its sodium salt. At all dosage levels of both compounds, the rats developed diarrhea, which increased in intensity with increasing dosage and interfered with the proper collection of urine. Death occurred as a rule within 48 hours after drug administration. At autopsy the most significant finding was the large fluid content in all parts of the gastro-

intestinal tract, which appeared yellowish and transparent in the small intestines. All other organs except for some congestion seemed normal macroscopically and revealed no substantial pathological changes upon microscopic examination. The approximate oral  $LD_{50}$  of both compounds lies around 14 gram/kg. body weight.

The intraperitoneal toxicity of sodium phthalylsulfacetimide was somewhat higher than the oral toxicity. However, it still remained on a rather low level as can be noted from the figures in the lower part of Table III. The  $LD_{50}$  seems

TABLE III  
*Oral toxicity in rats*

DRUG	DOSE <i>gm./kg.</i>	NO. OF RATS	NO. OF DEAD	PER CENT DEATH
Sodium phthalylsulfacetimide	15	20	12	60
	14	10	6	60
	13	10	4	40
	12	10	1	10
	10	20	0	0
	5	10	0	0
Phthalylsulfacetimide	15	10	9	90
	13	10	2	20
	12	10	0	0
	10	10	0	0
	8	15	0	0

*Intraperitoneal toxicity in rats*

Sodium phthalylsulfacetimide	12	10	9	90
	10	10	7	70
	9	13	0	0
	8	15	0	0
	5	10	0	0
	4	10	0	0
	3	10	0	0

to lie near 10 gram/kg. body weight. This is the more remarkable since absorption from the peritoneal cavity was rather extensive (to be shown later). A fatal dose caused death always within the first 24 hours, sometimes as soon as 1-2 hours after the injection. Introduction of the drug in 20% concentration into the peritoneum immediately caused spasm of the abdominal muscles and was obviously painful. A period of general depression followed. Shortly before death the animals went into repeated convulsive seizures, interrupted by a lethargic state with labored breathing. Finally complete side position was maintained, the reflexes disappeared and death ensued. Autopsy revealed in all instances large amounts of yellowish, slightly blood tinged fluid

in the peritoneal cavity (unabsorbed drug). All abdominal organs were congested and both the parietal and visceral layers of the peritoneum contained numerous petechial hemorrhages, suggesting death due to asphyxia. The kidneys were of normal size and consistency and no crystals were seen in cross sections.

*b. Subacute Toxicity.* Ten albino rats were given 10 gram/kg. of sodium phthalylsulfacetamide daily for a period of 5 days by stomach tube. Although they developed diarrhea and showed considerable depression, all animals sur-

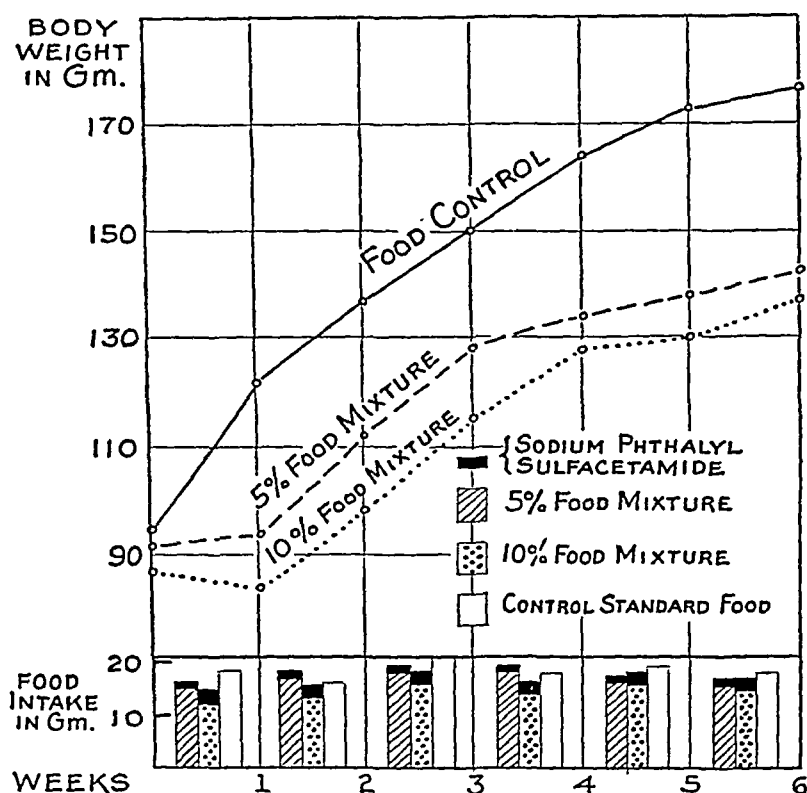


FIG. 2. CHRONIC TOXICITY IN ALBINO RATS

vived without apparent ill effects. They were killed one week after termination of the experiment at which time they had completely recovered. At autopsy all organs appeared normal.

*c. Chronic Toxicity.* The results of experiments with food mixtures containing sodium phthalylsulfacetamide are summarized in Fig. 2. All figures represent the mean of the values of 20 animals in each of the food mixtures and of 10 rats in the control group. It can be seen that the animals on the 10% as well as on the 5% food mixture showed a retarded gain in weight as compared to litter mates eating the pure standard food. It is also apparent from the bars at the bottom of the graph that the daily food consumption is not mate-



rially impaired by a 5% content of the drug and only slightly more inhibited by the mixture of 10% sodium phthalylsulfacetimide. All animals on the drug diet showed definite diarrhea. The symptom was constant throughout the duration of the study and was more pronounced with the higher drug concentration. In this connection, it seems of interest that the symptom of diarrhea was also observed in comparative studies with a 10% food mixture of succinyl-sulfathiazole where it resulted in a similarly retarded gain of body weight. Apparently the constant diarrhea interfered with the proper utilization of the food. Decreased production of certain vitamin and growth factors by depression of the normal bacterial flora of the gut must also be considered as a possibility in this connection <sup>15-18</sup>.

Only traces of sulfonamide were found in the blood with both concentrations of sodium phthalylsulfacetimide in repeated checkups throughout the six weeks period. Despite the constant and considerable contamination of 24 hour urine specimens with liquid stools, the total sulfonamide recovered in these "urine specimens" never exceeded 10% of the ingested amount. On the lower dosage level, where better separation of stool and urine could be accomplished in some instances, the daily urinary excretion of phthalylsulfacetimide was found to be below 1% of the intake, confirming the rather insignificant absorption of this sulfonamide into the blood stream.

The nonprotein nitrogen levels remained within the normal range at the completion of the experiment and complete blood counts (hemoglobin, red blood cell, white blood cell, and differential counts) showed no material deviation from the normal values established in these animals at the start of the toxicity study.

All rats were killed after completion of the experiment and their organs examined macroscopically and in stained sections under the microscope. With the exception of the gastrointestinal tract, which appeared atonic and distended and contained considerable amounts of clear, amber colored fluid in the small intestines, as well as semiliquid stools in the large bowels, no organs revealed any substantial differences from those of normal control animals.

### *3. Absorption and Excretion*

*a. Animals.* The striking difference of enteral and parenteral absorption of sodium phthalylsulfacetimide is clearly brought out in Table IV. Low blood levels are obtained in rabbits after the oral administration of 2 gram/kg. of the drug, whereas the same amount produces high blood concentrations after subcutaneous and intraperitoneal injection. In fact, three hours after administration by either of these routes the levels are as good as after intravenous injection, pointing to rapid absorption from parenteral sites. Essentially similar results were found in the rat with the 5 gram/kg. dose. Since only

traces of "free" drug were found in the blood of both animal species despite the high drug concentrations, it seemed established that no substantial splitting of this compound occurs in the living tissues.

The rapid disappearance of the drug from the blood, as depicted in Table IV, as well as the excessive urine concentrations observed, suggest speedy elimina-

TABLE IV  
*Total blood and urine concentrations in rabbits and rats after administration of sodium phthalylsulfacetimide by various routes*

ANIMALS	HOURS	PER OS	SUBCUTANEOUS	INTRAPER-ITONEAL	INTRAVENOUS
Rabbits  2 gm./kg.		Blood levels			
		mg. %	mg. %	mg. %	mg. %
		4.0	26	59	97
		3.2	36	33	30
	8	0	10	0	0
		Urine levels			
		Diarrhea contamination			2240
			1680	2170	482
			114	975	121
Rats  5 gm./kg.		Blood levels			
		0	55	108	
		0	31	69	
		0	0	0	
		Urine levels			
		Diarrhea contamination		4900	
				2700	
			6800	140	

The figures for each route of administration represent the mean values from 3 rabbits and 5 rats.

tion of the phthalyl compound after glomerular passage due to insignificant tubular reabsorption. While only minimal amounts of phthalylsulfacetimide were found in the urine after *oral* administration of the sodium salt, 50–70% of this drug could be recovered from the urine of rats and rabbits within 24 hours after subcutaneous, intraperitoneal or intravenous injection. These figures were found to compare well with the values for the urinary elimination of parenterally administered sulfadiazine.

*b. Humans.* Three male subjects were given a single dose of 10 gram of

sodium phthalylsulfacetimide dissolved in one glass of water. None of the individuals experienced any discomfort from this large dose and none showed any measurable blood levels at the four intervals tested. This was in agreement with the negligible urinary elimination which reached only 1.2% of the administered dose after 24 hours (Table V).

TABLE V

*Absorption and excretion of sodium phthalylsulfacetimide in man*

(Each of three adult subjects received 10 grams of the drug in aqueous solution by the oral route.)

	1 HOUR	4 HOURS	8 HOURS	24 HOURS
Blood, mg. %.....	0	0	0	0
Urine, % excretion.....	0	0.3	0.5	1.2

TABLE VI

*Concentration of dissolved sulfonamide in contents of gastrointestinal tract 4 hours after stomach tube feeding in rabbits*

DRUG	TISSUE	APPROXIMATE pH NITRAZINE PAPER	SULFONAMIDE  mg. %	REMARKS ABOUT FILTRATION
Sodium phthalylsulfacetimide. 2.28 gm./kg. Dissolved in 60 cc. of water	Stomach			Semisolid contents. No filtrate obtained
	Jejunum	>7.5	1360	Whatman #2 filter paper
	Ileum	>7.5	2180	Whatman #2 filter paper
	Colon	7.0	3200	Whatman #4 filter paper
	Blood		7.6	
Sodium sulfadiazine. 1.4 gm./kg. Dissolved in 60 cc. of water	Stomach	<4.5	77	Whatman #2 filter paper
	Jejunum	7.5	77	Gauze only!
	Ileum	>7.5	114	Gauze only!
	Colon	7.0	370	Gauze only!
	Blood		50	

#### 4. Gastrointestinal Tract

*a. Sulfonamide Concentration in the Contents of the Gut.* Equimolar amounts of sodium sulfadiazine and sodium phthalylsulfacetimide dissolved in equal volumes of water were administered to fasting rabbits by stomach tube. After three hours the same amount of water was readministered and the animals were killed one hour later.

The results of these experiments on 4 rabbits are illustrated in Table VI. Since sodium sulfadiazine cannot remain in solution at the pH of the stomach nor be redissolved to a significant extent at the moderately alkaline surrounding of the small intestines, the low concentration of this sulfonamide can be ac-

counted for by the poor solubility of its free compound (12 mgm. % in water at body temperature). Sodium phthalylsulfacetimide might also be precipitated out in the strongly acid contents of the stomach but phthalylsulfacetimide apparently is redissolved with ease when it enters the slightly acid or alkaline contents of the small bowel, which seem quite adequate for the formation of the sodium salt (see Tables I and II). Thus, concentrated solutions of the phthalyl compound are created in the small bowel. Even higher concentrations were found in the colon, possibly because of the reabsorption of water in this region.

Despite these high levels in the gut contents, the blood concentration of the phthalyl compound is almost seven times lower than that of sulfadiazine. Hence, the degree of solubility in water and the absorbability through the intestinal mucosa into the blood stream are by no means closely interdependent.

It should be pointed out that in some instances the intestinal contents were redetermined after standing at room temperature for 24 hours. No substantial cleavage of the phthalyl compound was observed in any of these tests. It should also be realized that our determinations tend to favor sulfadiazine in the comparison with sodium phthalylsulfacetimide. Since we were unable to obtain filtrates from the gut contents containing sulfadiazine and had to use the fluids after passage through gauze only, possible contamination with undissolved drug could not be excluded.

The table conveys the merits of a compound which is highly soluble at the normal pH ranges of the intestinal tract and prevented from entering the blood stream by its specific configuration. It is obvious that for bacteriostasis in the gastrointestinal tract such compounds should possess decided advantages over absorbable agents even though their antibacterial effect may be less spectacular on a gram per gram basis, since as is exemplified in this experiment, absorbable sulfonamides are present in the intestinal tract in concentrations which are minimal if compared with the levels of sodium phthalylsulfacetimide. This might be due in part to the poor solubility of most absorbable sulfonamides and partly to the fact that they rapidly enter the blood stream and are thereby prevented from accumulating in the lumen of the bowels.

*b. Sulfonamide Concentration in the Wall of the Gut.* Fifteen rabbits were used in these experiments. The concentration of sodium phthalylsulfacetimide in the various layers of the intestinal wall was determined simultaneously with the blood concentration 3, 6, and 17 hours after intubation of the drug. Equimolar amounts of sodium sulfadiazine were used in all instances in control animals for the comparison of the behavior of an absorbable compound.

It can be stated that after removal of the mucosa, the muscularis and the serosa were found to contain about the same concentration of sulfonamide as the intact gut. In fact, the variations in tissue concentration of the three lay-

ers were so minimal that they could be neglected in most instances. Minor variations were not surprising and were actually expected because of the slightly different location of the pieces used for determination.

Table VII illustrates the study at the three hour interval with groups of three rabbits each; the results obtained were found to be representative also for the other two time intervals, with the exception of generally lower sulfonamide levels due to the increased span between drug administration and determination.

The table summarizes the results with the intact mucosa. They applied in like manner to muscularis and serosa. Separate illustration of the latter results was, therefore, omitted. In comparison to the low blood level of sodium

TABLE VII

*Sulfonamide concentration in the intestinal wall 3 hours after oral drug administration in rabbits*

DRUG	TISSUE	TOTAL SULFONAMIDE
		mg. %
Sodium phthalylsulfacetimide, 5 gm./kg.	Stomach	82.4
	Jejunum	139.7
	Ileum	171.0
	Colon	63.7
	Blood	7.8
Sodium sulfadiazine, 3.1 gm./kg.	Stomach	46.8
	Jejunum	50.6
	Ileum	78.9
	Colon	29.7
	Blood	77.0

phthalylsulfacetimide, the levels in all parts of the gastrointestinal wall must be considered very high. In contrast it can be noted that the sulfadiazine blood level is about 10 times higher than that of the phthalyl agent and that this concentration is not surpassed for sulfadiazine anywhere in the tissues of the gut. Roughly, the sulfadiazine tissue concentration is about half that of the sodium phthalylsulfacetimide levels. Both drugs show the identical pattern: low concentration in the stomach, rising in the jejunum, peak in the ileum and lowest level in the colon. If one compares the findings with those in Table VI, some correlation between drug concentration in the gut contents and the intestinal wall seems apparent for the stomach, jejunum and ileum for both phthalylsulfacetimide and sulfadiazine. The colon, on the other hand, despite the highest drug concentrations in its contents, seems unable to permit the same extent of diffusion as the small bowel, possibly because of the entirely different histological structure of its mucosa. The large bowel is, after all, essentially an *excretory* organ.

The studies suggest that the production of high N<sup>4</sup>-phthalyl sulfonamide concentrations in the intestinal wall is not dependent upon high blood levels but can be achieved satisfactorily by means of simple diffusion from the lumen of the gut.

*c. Sulfonamide Diffusion Through the Isolated Gut.* It was just demonstrated that the phthalyl compound is apparently able to penetrate through the mucosa into the deeper layers of the gut. The experiments to be discussed were designed to test this ability of diffusion by some other means and to substantiate the observation that a substance which obviously is unable to enter the bloodstream may diffuse through all layers of the intestinal wall.

TABLE VIII  
*Diffusion of sulfonamide through isolated surviving loops of rat gut in 2 hours*

DRUG	MG. PUT INTO LOOP	AMOUNT DIFFUSED INTO RINGER BATH	PERCENTAGE DIFFUSION
		mg.	
Sodium phthalylsulfacetimide, 4% aqueous solution.....	120	21.0	17.5
Sodium sulfadiazine, 2.5% aqueous solution.....	75	15.8	21.0
Phthalylsulfacetimide			
a) 10% aqueous suspension.....	300	6.0	2.0
b) powder.....	Excess	5.5	
Sulfadiazine			
a) 10% aqueous suspension.....	300	0.3	0.1
b) powder.....	Excess	0.3	
Sulfathiazole, 10% aqueous suspension.....	300	0.7	0.2

Each value represents the average of two experiments.

Table VIII contains the results of comparative tests with the phthalyl compound and absorbable sulfonamides. Solutions of the sodium salts were employed in equimolar amounts, whereas this arrangement was deemed unnecessary with the powder and suspension of phthalylsulfacetimide, sulfadiazine and sulfathiazole, since it was intended to test their comparative readiness to enter into solution from an undissolved excess.

It is apparent that sodium phthalylsulfacetimide in *solution* penetrates about as readily as sodium sulfadiazine into the Ringer bath. When the sparingly soluble phthalylsulfacetimide is introduced into the gut as dry powder, or as a finely divided watery suspension, diffusion is far better than from sulfadiazine or even from sulfathiazole under the same experimental conditions. This observation is explainable by the fact mentioned previously that at the pH

of the gut (or the Ringer solution) the phthalyl agent will readily form the soluble sodium salt whereas sulfadiazine or sulfathiazole will dissolve much slower and only as the "free" acid. In line with this interpretation, sulfathiazole, which is far more soluble than sulfadiazine (96 mgm.% as compared to 12 mgm.% at body temperature) shows also somewhat better diffusion from the suspended state.

#### DISCUSSION

From the aspect of the pharmacologist, sodium phthalylsulfacetimide appears to possess many desirable features of a gastrointestinal antiseptic. It is highly soluble in the intestinal contents and reasonably stable in the physiological pH range of this organ system. It is only sparingly absorbed into the blood stream when administered orally and yet it may diffuse into the tissues of the intestinal wall. Any amount of the drug entering the blood is rapidly eliminated by the kidneys.

The intraperitoneal toxicity of sodium phthalylsulfacetimide was found to be surprisingly low, in view of the fact that rapid and extensive absorption of the drug takes place from any parenteral site, resulting in excessive blood concentrations. In this connection it seems of interest to compare our findings with some results reported by other investigators for phthalylsulfathiazole.

Poth and Ross<sup>4</sup>, injecting a suspension of phthalylsulfathiazole intraperitoneally into dogs, found an LD<sub>50</sub> of 2.5 gram per kg. body weight. In agreement with our observations, these authors also noted discomfort and spasm of abdominal muscles when a 10% solution of the sodium salt was introduced into the peritoneal cavity. Since the sodium salts of "free" sulfathiazole or sulfacetimide do not produce this picture, the symptoms seen after the introduction of N<sup>4</sup> acylated compounds seem to be due to the presence of the phthalic acid radical. Mattis, Benson and Koelle<sup>5</sup> reported that phthalylsulfathiazole given to female white mice in a dose of 10 gram per kg. gave no symptoms of toxicity. However, when they injected the sodium salt of this compound intraperitoneally, the LD<sub>50</sub> was 0.8 gram per kg. body weight. The picture of acute toxicity was similar to the one that we observed in rats with sodium phthalylsulfacetimide.

Although results in mice and rats are not directly comparable, they show in general good correlation. Hence, the acute oral toxicities of the two phthalyl agents can be considered similar, whereas the intraperitoneal toxicities are substantially different, phthalylsulfathiazole being about ten times as toxic as phthalylsulfacetimide. Since there is little absorption of either drug after intubation, it is obvious that the results of *parenteral* administration are representative of true toxicity relationships. The considerably higher intraperitoneal toxicity of phthalylsulfathiazole seems explainable by the fact that the toxicity of "free" sulfathiazole is about seven times as great as that of sulfacet-

imide<sup>19, 20</sup>. Hence, should extensive absorption occur from ulcerations of the intestinal wall, as it happens in therapeutic usage, one should have less to fear from high blood levels of phthalylsulfacetamide than from those of phthalylsulfathiazole.

It should also be pointed out that the mere presence of large amounts of a sulfonamide compound in the intestinal contents or in the stools is no indication of the value of such an agent as a gastrointestinal disinfectant, unless proof can be presented that a substantial part is present in *dissolved* form. Obviously no antibacterial activity can be expected from undissolved substances.

Finally, the demonstration that a "nonabsorbable" sulfonamide is able to diffuse from the lumen of the gut into and through all strata of the intestinal wall, although it is barred from entering the blood stream by this same route, strengthens the concept of intestinal absorption as an elective and "vital" mechanism of specific cell structures, which has to be clearly distinguished from the passive process of simple diffusion<sup>21</sup>.

It seems hardly necessary to discuss the advantages of a highly soluble but "nonabsorbable" sulfonamide in the treatment of many bacterial infections which are strictly localized in the gastrointestinal tract and to dwell upon the particular usefulness of such an agent in pre- and post-operative surgery where high sulfonamide levels in tissues other than the gut would constitute a superfluous risk to the patient.

#### SUMMARY

1. The toxicity of sodium phthalylsulfacetamide, as well as the absorption and excretion of this compound from various routes of administration, and its behavior in the gut was investigated.

2. The intraperitoneal toxicity in albino rats was found to be surprisingly low. The approximately LD<sub>50</sub> was estimated as 10 gram per kg. as compared to an LD<sub>50</sub> of 0.8 gram per kg. for sodium phthalylsulfathiazole reported in white mice.

3. Sodium phthalylsulfacetamide is highly soluble at the physiological pH range of the intestinal tract. After oral administration this drug is present as a highly concentrated solution in the contents of the small and large bowel. Although absorption into the blood stream from the lumen of the gut is minimal, considerable amounts diffuse into the deeper strata of the intestinal wall.

4. When injected parenterally the compound readily enters the blood and is rapidly eliminated by way of the kidneys.

5. The findings indicate that sodium phthalylsulfacetamide possesses many desirable properties of an intestinal antiseptic.

The technical assistance of Helen and Ruth Salzberg is gratefully acknowledged.



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## ACID-NEUTRALIZING POWER OF SEVERAL PROTEIN HYDROLYSATES AND OTHER SUBSTANCES USED IN ULCER THERAPY\*

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The current popularity of feedings of protein hydrolysate in the therapy of peptic ulcer dates from the report of Co Tui et al<sup>1</sup>. They found that hyperalimentation with a high caloric and high amino acid (protein hydrolysate) mixture was efficacious in bringing acute peptic ulcers to a state of quiescence. This result was attributed to the fact that the protein hydrolysate given (Amigen in 29 cases, Squibb's Protein Hydrolysate in 1 case) acts simultaneously as an antacid and as a rich source of nutriment from which tissues can easily be rebuilt. The antacid properties of one of these hydrolysates had been demonstrated in 1942 by Levy and Siler<sup>2</sup>, who used a test meal of a 10% Amigen solution on 48 normal subjects, and then studied the acidity of gastric specimens every 10 minutes for as long as one and a half hours. In 30 of these subjects, the solution was buffered with 0.1N NaOH to a pH of 6.6 before administration; in the other 18, it had a pH of 4.5 without additional buffer. They concluded that, "Amigen is an effective buffering agent. pH values as determined in 18 subjects (after unbuffered Amigen) are well within the range of pH in which free acid is not present, and peptic activity reduced to a minimum." Because of the antacid property of this protein hydrolysate and its value as a potent source of amino nitrogen for body metabolism, it was suggested by these authors that "Amigen be used in the clinical management of peptic ulcer even in the presence of bleeding." Since the foregoing work was published, other investigators have recognized this dual role of protein hydrolysate feeding in ulcer therapy<sup>2, 3, 4</sup>, but its antacid efficacy has always been demonstrated clinically and by the use of only one particular preparation. Hence in the present work, a comparative evaluation has been made of the buffering action in vitro of four different protein hydrolysates. Also, for purposes of comparison, a number of other substances commonly used as antacids in ulcer therapy have been similarly studied.

### METHOD

The substances included in the present study are shown in Table I. Of the four commercial protein hydrolysates, two (Amigen and Squibb's Protein Hydrolysate) were derived from casein by pancreatic digestion, one (Lactamin)

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from lactalbumin also by digestion with pork pancreas, and one (Essenamine) from lactalbumin by hydrolysis with NaOH. Commercial casein was studied as an example of an unhydrolyzed protein. Unfortunately, a similar preparation of lactalbumin was not available. The Hi-Pro Milk Powder is a dried cow's milk preparation, whereas the Zoymilk Powder is derived from soybeans. In every case 1 gm. of solid was employed for a titration, except  $\text{NaHCO}_3$  of which only 0.1 gm. was necessary because of its high neutralizing power. Of the liquids, 5 cc. of approved fresh whole milk and 1 cc. of Amphojel (an alumina gel preparation) were the minimum quantities which gave a conveniently measureable neutralizing action under the conditions of the experiments. In

TABLE I  
*Buffer values of various substances, between their initial pH's and 3.5*

SUBSTANCE	INITIAL pH	TITER (cc. 0.1 N HCl)
Amigen*	5.55	14.2/g.
Essenamine†	7.15	4.7/g.
Lactamin‡	5.50	18.1/g.
Squibb's Protein Hydrolysate§	6.05	15.3/g.
Casein	5.50	5.3/g.
Whole fresh milk	6.89	0.8/cc.
Amphojel	6.69	13.9/cc.
Hi-Pro Milk Powder	5.12	7.0/g.
Zoymilk Powder	6.40	9.4/g.
Sodium bicarbonate	8.25	132/g.

\* Pancreatic hydrolysate of casein (total N—12%; amino N—7.8%; ash 5.5%).

† NaOH hydrolysate of lactalbumin (total N—12.5%; amino N—8%; ash 1.9%).

‡ Pancreatic hydrolysate of lactalbumin (total N—11.5%; amino N—7.5%; ash 4%).

§ Pancreatic hydrolysate of casein (total N—13.5%; amino N—3%; ash 5.5%).

every case the measured quantity of substance was mixed with enough distilled water to make the total volume 25 cc. Most of the substances went into solution easily; Essenamine, milk, and Amphojel formed suspensions and were titrated as such.

For the titrations, an ordinary 10 cc. burette and glass electrode assembly were employed. Following measurement of the pH of the freshly prepared solution, carefully standardized 0.1N HCl was added in small volumes, and the pH was redetermined after each such addition—until a pH of 2.5 or lower was attained. Two minutes of stirring the solution by hand after each addition of acid was found sufficient to stabilize the pH of the resultant mixture for all but 3 of the substances. Essenamine and  $\text{NaHCO}_3$  required 10 minutes for attainment of equilibrium each time—the former because of its undissolved state, the latter because of its slow loss of  $\text{CO}_2$  from solution.

The alumina gel titrations posed a special problem because of characteristically slow neutralization over a prolonged period of time. Moreover, no matter how thorough the mixing of the suspension before titration, it was difficult to get duplicate titrations to agree as well as they did for the other substances, because the pH values practically never became stabilized after addi-

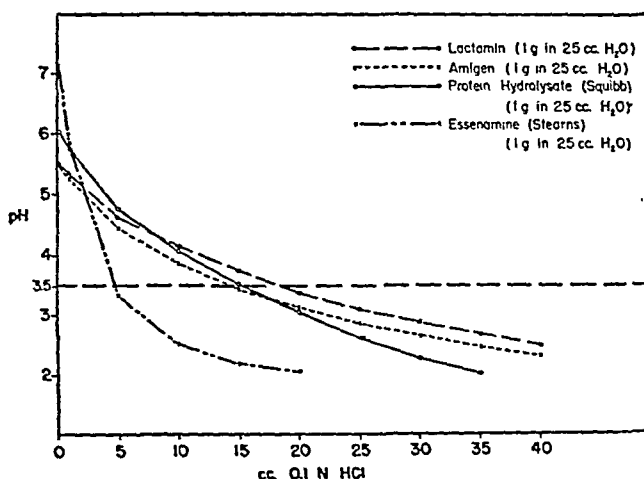


FIG. I. ELECTROMETRIC TITRATION CURVES

Each curve is an average of 4 titrations.

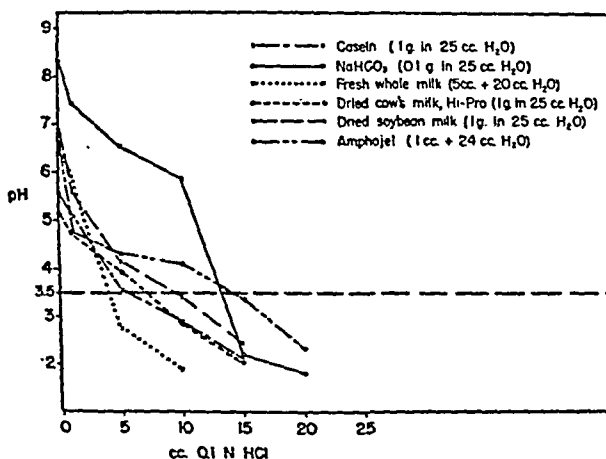


FIG. II. ELECTROMETRIC TITRATION CURVES

Each curve is an average of 4 titrations, except for the two milk powders which represent single determinations.

tion of HCl, but continue to rise very slowly upon standing. Even two hours after each acidification the pH still showed a slow drift toward the alkaline side, sufficient to invalidate the standard titration technique when applied to this preparation. Consequently, a somewhat different method of titration was employed for the Amphojel than for the other substances. Instead of making successive additions of the acid to a single specimen until a pH well below

2.5<sup>-</sup> was obtained, measured amounts of HCl (e.g., 1, 5, 10 cc. etc.) were added to each of several specimens of Amphojel of equal volumes in different beakers. Then, after at least two hours of stirring, the pH was measured and recorded. Sometimes, the total volume of acid was added in two parts, with 2-hour stirring and a pH determination after each addition. The agreement between the pH's obtained by these two techniques was good enough to warrant using an average of the results obtained by both methods.

The data were plotted as shown in figs. I and II. Apart from the data for Amphojel, the agreement among quadruplicate determinations was invariably well within  $\pm 0.1$  pH, and in most instances it was within  $\pm 0.05$  of a unit. For purposes of analysis, each such set of quadruplicate pH's, corresponding to any one volume of added HCl, were averaged, and the mean values used for the graphs. Only in the cases of the dried cow's milk and soybean milk preparations, was a single series of determinations performed. From the resulting curves, the volume of HCl necessary to bring the pH down to a value of 3.5 was obtained by interpolation. This pH-value was chosen because it corresponds to 1 mN free HCl, and therefore virtually to complete neutralization of the substance without any excess free acidity.

The results are summarized in Table I. Three of the four protein hydrolysates manifested a relatively high neutralizing power down to pH 3.5, whereas the fourth combined with only about one quarter the amount of acid required by the most effective of these substances. Thus, 1 g. of Lactamin required 18.1 cc. of 0.1N HCl per gram of powder, Squibb's Protein Hydrolysate 15.3 cc., Amigen 14.2 cc., and Essenamine 4.7 cc. Casein, the source material for two of these preparations took only 5.3 cc. of the reagent—about  $\frac{1}{3}$  of that required by the corresponding hydrolysates.

The value for the dried cow's milk (7.0 cc.) was only 35 per cent greater than for the casein, but significantly less than that for the soybean preparation. In contrast with these values, the fresh whole milk took up only 0.8 cc. of acid per cc. of undiluted milk, whereas Amphojel was more than 17 times as potent (13.9 cc.).

#### COMMENT

It is evident from these results that at least 3 of the protein hydrolysates have sufficient acid-neutralizing power (to pH 3.5) to be effective when taken by mouth in quantity. Thus, a 300 g. daily dose of the most potent of these preparations (Lactamin)—the minimum daily amount usually administered by Co Tui—is capable of neutralizing almost 5.5 liters of 0.1N HCl. The others will take up 4.6, 4.3, and 1.4 liters per 300 g. respectively. In contrast with these values, 5.5 liters of acid will require about 45 g. of  $\text{NaHCO}_3$ , or about 10 level teaspoonfuls.

There does not seem to be any clear-cut relationship between the buffering power of these hydrolysates and their content of total or amino nitrogen, or ash (see Table I). The manner in which the hydrolysate is prepared seems to be significant, if one judges by a comparison of the data for the casein hydrolysates prepared with pork pancreas and NaOH. However, too much weight must not be attached to this implication of the data without substantial confirmation. It is interesting that the extent of hydrolysis of casein attained in these preparations results in no more than a 3-fold increase in neutralizing power. Were the reaction carried clear through to the amino-acid stage, the increase would undoubtedly have been considerably greater.

Taking into consideration the average daily doses of Amphojel and the protein hydrolysates, as well as their buffer capacity per unit quantity, the latter are seen to be superior in their per diem antacid action to the nonabsorbable alkali. It is evident, therefore, that the acid-neutralizing function of the protein hydrolysates must be of major importance when they are used in ulcer therapy, and that their efficacy in this disease cannot be ascribed wholly to their nutritive value.

#### SUMMARY

Buffer curves were determined for four commercial protein hydrolysates and a number of other substances commonly used in the therapy of peptic ulcer, i.e., whole fresh milk, a pharmaceutical alumina gel preparation, and sodium bicarbonate. For purposes of comparison, unhydrolyzed casein, a dried whole milk powder, and a soy milk powder were also included in the study. The procedure entailed electrometric titrations with 0.1N HCl under standardized conditions, using a glass electrode. Buffering power between the initial pH and pH 3.5 was estimated by interpolation from the titration curves, the lower limit being that employed in this laboratory as the boundary value between free and combined gastric acidities.

At least three of the protein hydrolysates were found to have sufficient acid-neutralizing power to be effective antacids when taken by mouth in a dose of 300 g. distributed throughout the day—the minimum amount administered by Co Tui in his hyperalimentation treatment for peptic ulcer. Whereas 300 g. of the most effective of these preparations neutralized almost 5500 cc. of 0.1N HCl *in vitro*, this amount of acid required 45 g. (about 10 level teaspoonfuls) of  $\text{NaHCO}_3$  to bring its pH to 3.5. Furthermore, on this per diem basis, the protein hydrolysates were found to be generally superior even to the alumina gel preparation investigated, which has been demonstrated to be an effective antacid both *in vitro* and *in vivo*. As for the other substances studied, none of them were comparable in their acid-neutralizing action even to the alumina preparation.

It is concluded, therefore, that the acid-neutralizing function of the protein hydrolysates is of major importance when they are administered orally in ulcer therapy. If they also possess a definitive nutritional function in the healing of ulcer, the mechanism still awaits elucidation.

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## IS PARIETAL CELL SECRETION INHIBITED BY ACIDOSIS?\*

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The secretion of hydrochloric acid by the stomach is influenced by many factors, with the chief interest centering on hormones and on stimuli, which are mediated by the nervous system. Among other influences may be mentioned dehydration<sup>1</sup>, hyperpyrexia<sup>2</sup>, anoxia<sup>3</sup>, anemia<sup>4</sup>, and the CO<sub>2</sub> content of the plasma.

Apperly<sup>4</sup> felt that he had established a direct linear relation between the bicarbonate content of the blood and the gastric chloride level. The "rebound effect" of administering soluble alkalis to humans lends some support to this opinion. Kiefer<sup>5</sup> studying gastric secretion in peptic ulcer patients, whose plasma CO<sub>2</sub> was varied by the ingestion of sodium bicarbonate, could not verify Apperly's findings.

In acute experiments on dogs, Browne and Vineberg<sup>6</sup> reported that vagal gastric secretion was inhibited, when the CO<sub>2</sub> content of the arterial plasma fell below 30 vol. % but that histamine, *if given prior to the induction of acidosis*, could still exert its usual effect at levels below 30 vol. %. However, in the presence of acidosis already established, they were unable to elicit acid secretion by histamine, until after bicarbonate of sodium had been given intravenously. They also found no relation between the pH of the arterial plasma and the secretory response of the stomach. Babkin<sup>7</sup> has supported these conclusions. On the other hand, Taylor and Michael<sup>8</sup> found no relation between plasma CO<sub>2</sub> and gastric acidity in Pavlov pouch dogs, in which they had produced acidosis of severe degree by ammonium chloride. Indeed they reported an increased volume of acid secretion in the pouch of the acidotic dog, which they attributed to "a coincidental water intake from thirst produced by salt (ammonium chloride) ingestion". Our studies tend to confirm the findings of the latter investigators.

It seems curious that there are so few records of gastric secretion studies in clinical states of acidosis. In order to test Browne's theory that an acidosis of severe degree (below 30 vol. %) will inhibit both psychic (vagal) and chemical (histamine) phases of parietal cell secretion, the following observations were made.

### METHODS

The gastric acid was titrated in the usual manner against N/10 NaOH with Topfer's reagent and phenolphthalein, and the results were recorded as clinical

\* Acknowledgement is gratefully made of the helpful advice of Dr. E. S. Nasset, Professor of Physiology, Department of Physiology and Vital Economics, and of the assistance given by R. A. Russell, Research Fellow of this department, in the animal experiment.



units. Both in the human and animal material the usual errors of salivary and duodenal neutralization were unavoidable as was the impossibility of assurance that the stomach had been completely emptied. Hence it was not practical to estimate the actual volume of parietal secretion, as is often done, by multiplying the titration units by the volume of the sample obtained. The  $\text{CO}_2$  content was determined on serum, collected and centrifuged anaerobically, by the method of Van Slyke and Neil as outlined in Peters and Van Slyke<sup>9</sup>. Venous blood, not "arteriolized", was drawn. The chlorides of the serum and gastric juice were determined by the method outlined by Van Slyke and Sendroy<sup>9</sup>.

#### CLINICAL OBSERVATIONS

##### *Pulmonary Fibrosis*

Two individuals suffering from fibrosis of the lung, who had the syndrome of alkalosis (high  $\text{CO}_2$  serum content) and polycythemia did not produce HCl on histamine stimulation. In this connection it is interesting that the infants with congenital alkalosis and diarrhea, described by Gamble<sup>10</sup> and Darrow<sup>11</sup> did not have hyperacidity.

##### *Diabetic Acidosis*

H. G., a colored male 46 years of age was brought into the Municipal Hospital on 11-26-47. As on his previous admissions he had become careless about his diet and stopped taking insulin. He presented the usual findings of severe acidosis but was not in coma. Because of gastric distension and vomiting, Wangensteen suction was instituted soon after his admission, so that it was possible for us to secure a sample of gastric juice at the time when his blood was taken for chemical analysis. The gastric juice had 28 units of free HCl, 47 units of total acid, while the serum  $\text{CO}_2$  content was 17 vol. %, chlorides 98 m.eq./l.

One week later, having recovered from his acidosis, a conventional histamine analysis was performed. On this occasion the serum  $\text{CO}_2$  content was 61 vol.% and the free HCl of the 30 minute sample was 55 units.

##### *Chronic Renal Acidosis*

Six individuals in terminal uremia failed to secrete HCl in response to histamine stimulation. Two other patients with chronic renal acidosis, who were much improved at the time of their discharge, also failed to produce HCl with histamine. In Table I there are listed five individuals who secreted variable amounts of HCl, either spontaneously or as a result of histamine stimulation. The sixth patient, P. M., was treated with citric acid and sodium citrate. He came out of acidosis briefly but was otherwise unimproved.

However, he did not secrete HCl even when out of acidosis, suggesting that it was the uremic state rather than the acidosis which caused the inhibition.

### Experimental Acidosis

Human subject (V. W. L.)

Although ammonium chloride (Lilly enteric coated tablets) was ingested in doses of 20 gm. a day, severe acidosis was not achieved. Lethargy, nausea,

TABLE I  
Chronic renal acidosis

NAME	AGE	SEX	CO <sub>2</sub> CONTENT OF SERUM	CHLORIDES OF SERUM	N. P. N.	GASTRIC JUICE HCl UNITS*
			vol. %	m. eq.	mg. %	
M. P.	21	M	21	106	143	35
M. W.	30	F	29	109	69	16
J. H.	41	M	37	112	78	79
M. F.	43	M	36	113	72	26†
J. D.	59	M	25	108	94	87
P. M.	40	M	20	106	162	None
			46	98	154	None

\* 30 minutes after stimulant was given.

† No histamine was given to this patient.

TABLE II  
Experimental acidosis (human)

DATE	SERUM CO <sub>2</sub>	SERUM Cl	GASTRIC SECRETION 30' AFTER HISTAMINE		
	Vol. %		Volume	HCl units	pH
		m. eq.	cc.		
3-25-47	53.0	103	—	—	—
3-26-47		Ammonium chloride started—20 gm. daily			
3-27-47	49.0	107	81	81	1.25
3-28-47	36.5	110	90	84	—
3-31-47	37.0	111	*		

\* 12 hour retention of gross food occurred at this point.

muscle aching, marked diuresis and loss of weight attested to the absorption of the drug. It will be noted that even with a reduction of the serum CO<sub>2</sub> content of venous blood from 49 vol. % to 36.5 vol. %—a 25% reduction—no appreciable change occurred in the titration values of the gastric histamine juice (Table II).

### Animal Experiment

A 22.6 kg. female dog (# 18) was used in this experiment. This animal had had a subcutaneous intestinal implant<sup>12</sup> but was otherwise quite normal.

The implanted loop had failed to function. For the purposes of this experiment the dog was treated in much the same manner as a human, in order to avoid the criticism which attends an acute animal experiment.

After an overnight fast, the stomach was emptied of its fasting contents by a large gastric lavage tube. Histamine (1.13 mg.) was then given subcutaneously, and at the end of 30 minutes the stomach was again emptied. The fasting values of the acid secretion were variable, probably due to the fact that food stimuli were constantly present in the animal house. During

TABLE III  
*Experimental acidosis (dog)*

DATE	SERUM CO <sub>2</sub>	GASTRIC JUICE 30' AFTER HISTAMINE				
	Vol. %	Volume	HCl units	Total acid	pH	Cl m. eq.
Control period						
12- 8-47	57.0	67	95	103	—	151.0
12-10-47	50.5	35	109	115	1.06	151.0
12-12-47	53.5	46	95	101	1.05	146.9
12-15-47	52.0	25	90	107	1.46	148.2
12-17-47	47.8	32	80	86	1.12	140.2
12-21-47	54.8	44	92	101	1.47	147.2
Acidosis period (10-13 gm. ammonium chloride daily beginning Jan. 6th)						
1- 9-48	30.5	30	68	83	1.48	116.4
1-12-48	45.2	8	87	92	1.60	138.0
1-14-48	49.7	12	78	85	1.04	132.0
1-19-48	25.0	17	56	80	—	113.0
1-20-48	19.5	16*	44*	67*	1.32	—

\* Fasting specimen—no histamine given on this day.

the control period the "fasting" HCl values ranged between 5-30 units; during the acidosis period 10-65 units.

Following a control period, acidosis was induced by feeding ammonium chloride tablets, (Lilly) 10-13 gm. a day. Water was accessible to the dog during the daytime. On January 19th the dog refused food and vomited some of the tablets on the following day. She continued to drink water copiously. Recovery was prompt on cessation of the drug.

Table III shows the data obtained during the control and the acidotic phases. On Jan. 11 a shift from Lilly enteric coated tablets to another brand of enteric coated tablets caused the animal to come out of acidosis. On Jan. 14 the Lilly tablets were resumed. It will be noted that on the days of severe acidosis the animal secreted a considerable volume of HCl both with and without hista-

mine stimulation. It must be admitted, however, that both volume and titratable free acid diminished during the period of acidosis.

### DISCUSSION

It is clear from the foregoing that the parietal cell is able to secrete HCl in extreme acidosis. Both the diabetic and the young nephritic, as well as the dog, secreted HCl in response to histamine when the venous serum CO<sub>2</sub> content was well below 30 vol. %. The diabetic patient was able to secrete a considerable volume of HCl at a CO<sub>2</sub> level of 17 vol. % without histamine, as did the dog when her level was 19.5 vol. %. This suggests that even the vagus is capable of mediating stimuli to the parietal cells in the extremes of acidosis. When it is considered that a venous CO<sub>2</sub> content is always higher than the arterial level, doubt must be cast on the dictum of Browne and Vineburg regarding the inhibition of the parietal cells in acidosis.

It is true that the animal experiment listed above showed that diminished CO<sub>2</sub> content of the serum was accompanied by a decrease in the HCl of the stomach. Nevertheless acidosis, whether caused by diseased kidneys, or diabetes, or by ammonium chloride, results in a sick animal; and it would not be surprising that the parietal cell, as well as other cells of the body, suffered some impairment of function of a non-specific nature.

Further studies are contemplated to see if there is a direct relationship between the CO<sub>2</sub> content of the serum and parietal cell secretion in the pouch dog.

### SUMMARY

1. Clinical evidence is presented to show that parietal cell secretion is not abolished in chronic severe renal acidosis, nor in the acidosis of diabetes.

2. Histamine is capable of stimulating the parietal cell regardless of whether acidosis is induced before or after histamine is given.

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# Case Reports

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## A CASE OF SMALL INTESTINAL STASIS AFTER VAGOTOMY SUCCESSFULLY TREATED WITH URECHOLINE

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### CASE REPORT

The patient was a forty year old man who was admitted to the hospital complaining of epigastric pain, nausea and vomiting. He had been well prior to the events related below.

Four years before admission he first experienced epigastric pain, nausea and vomiting which occurred in episodes lasting one to five days. There was no hematemesis but a tarry stool was noted on one occasion. Three years ago, he was hospitalized because of these complaints. Gastrointestinal x-rays and gastric analysis were negative and his symptoms were relieved by diet and antacids. Occasional mild and transient attacks of pain and nausea recurred during the next two and one half years but these were ascribed to war conditions and no further diagnostic studies were made.

Four months ago he was again hospitalized because of severe abdominal pain. His epigastrium was quite tender. Complete blood count and urinalysis were normal. No occult blood was found in the stools. A chest x-ray and gall bladder series were negative. A gastrointestinal x-ray revealed a markedly deformed duodenum with a "fleck" of barium persisting in the six hour film. He was again treated with diet and antacids and was discharged after ten days. His symptoms, although still present, were improved.

In spite of careful attention to diet and medication, his symptoms recurred within a few weeks and he was again admitted to the hospital. Intensive medical treatment for a period of three months produced no lasting improvement and the x-ray picture was unchanged. Transabdominal vagotomy was performed under general anaesthesia. The operative procedure was not attended by any technical difficulties and his immediate postoperative course was satisfactory except for the appearance of a small area of atelectasis which cleared promptly under suitable treatment. His wound healed per primam. From the beginning however, he tolerated oral feedings poorly and complained of fullness, distension and crampy abdominal pain. Prostigmin and enemas were ineffectual and intravenous alimentation became necessary. A gastro-



FIG. 1. DILATED AND BARIUM FILLED STOMACH AND SMALL INTESTINE TWO WEEKS AFTER VAGOTOMY



FIG. 2. DILATED STOMACH AND SMALL INTESTINE SHOWN IN X-RAY TAKEN THREE DAYS AFTER FIG. 1



FIG. 3. MILLER-ABBOTT TUBE WITH ITS TIP IN THE CECUM



FIG. 4. NEARLY COMPLETE REVERSION TO NORMAL AFTER TREATMENT WITH URECHOLINE



intestinal x-ray, taken two weeks after operation, showed extensive dilatation of the stomach and small intestine (Fig. 1). A plain x-ray, taken three days later, revealed marked stasis (Fig. 2). Fluoroscopy disclosed that the stomach and intestine were not truly atonic but that there were segmental anti- and isoperistaltic contractions of short duration. These were largely purposeless movements which only succeeded in moving the barium mass to and fro. Although it was felt that there was no element of mechanical obstruction in this case, a Miller-Abbott tube was passed in order to definitely exclude this possibility. That the tube traversed the small intestine and passed into the cecum is shown in figure 3.

A transient improvement in distension and fullness followed the passage of the Miller-Abbott tube but the reinstitution of oral feedings resulted in the return of symptoms as before. By the sixth week after operation, it was felt that the patient had shown no tendency toward improvement. He had lost nearly twenty pounds in spite of efforts to maintain adequate nutrition. Accordingly, urecholine was given by mouth in a dose of ten milligrams, t.i.d., for a period of twenty-five days. Rapid improvement in his symptoms began at once and at the end of three weeks he had regained all his lost weight. He was allowed to leave the hospital one week later without medication. After a period of four weeks at home he returned to the hospital and reported that he had been well except for a few episodes of mild distension. Urecholine was again given for two weeks and no further symptoms appeared. He continued to gain weight. Gastrointestinal x-rays were repeated sixteen days after finally discontinuing the drug and they showed a nearly complete reversion to normal (Fig. 4). The patient remained asymptomatic without treatment for three months after these x-rays were taken and is presumed to have recovered completely.

#### COMMENT

There is ample proof that section of the vagus nerves frequently results in decreased motility of the stomach. Concerning the effects of vagotomy on the small intestine, there is less evidence. Cannon<sup>1</sup> reported that in vagotomized cats the motility of the small intestine was diminished. Moore<sup>2</sup> recently expressed the opinion that "changes in motility beyond the pylorus are transient, ill-defined and inconstant." That there may be some constancy to the effects of vagotomy on the small intestine is suggested by the work of Grimson and his associates<sup>3</sup>. They reported that x-ray studies of the small intestine in twenty-six patients who had been subjected to vagotomy showed delay in motility, a slight increase in calibre and a coarser mucosal pattern. The changes in these cases were apparently not sufficient to produce any clinical manifestations. Walters<sup>4</sup>, however, mentioned a patient who became distended on the fifth day

after vagotomy and who exhibited the typical x-ray findings of intestinal obstruction. At operation the small intestine was distended with fluid and air but in spite of the most careful search no mechanical obstruction was found. Machella<sup>5</sup> has seen a patient with small intestinal stasis after vagotomy which lasted about a week and responded well to urecholine.

It is difficult to correlate these findings with the well known tendency of patients to have diarrhea after vagus section, where the more rapid passage of food through the small intestine is generally thought to occur. The divergent effects of vagotomy may be reconciled on the theory that the intestine which has one of its central connections severed by vagotomy will be without an important governing mechanism and therefore more or less at the mercy of local conditions which may then produce these varying effects.

At any rate it would appear that dilatation and relative atonia of the small intestine may be a sequella of vagotomy in some patients. The administration of urecholine to these patients has been followed by recovery and the further use of this drug seems to be warranted.

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## CARCINOID TUMOR (ARGENTAFFINOMA) OF THE STOMACH

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### INTRODUCTION

The term carcinoid was first employed by Oberndorfer<sup>1</sup> to describe a tumor which resembled carcinoma histologically but not in behavior. Gossett and Mason<sup>2</sup> demonstrated that characteristically the cells of such tumors contain cytoplasmic granules which reduce silver ammonium oxide and suggested that the tumors arose from the Kultschitzky<sup>3</sup> cells in the base of the glands of Lieberkuhn. Because of the presence of the specific silver granules, the carcinoid tumor has also been called argentaffinoma. Originally it was thought that this tumor was benign and occurred almost exclusively in the vermiform appendix where the Kultschitzky cells predominate. Later reports, however show that carcinoid may occur anywhere from the stomach to the colon and that it makes up from 1.3 per cent to 1.8 per cent of all tumors of the gastrointestinal tract<sup>4, 5</sup>. It has also been found in the gall bladder<sup>6</sup> and ovary<sup>7</sup>. Malignant change has been found frequently in this tumor and is now considered to occur in about 30 per cent of all cases<sup>4</sup>.

The various names and classifications under which the neoplasm may be listed makes an exhaustive search of the literature difficult and always liable to error. To our knowledge, however, the present case represents the fifteenth of carcinoid tumor of the stomach reported and the sixth with symptoms and signs which led to operation and diagnosis. In nine subjects the tumor was discovered coincidentally at necropsy.

In 1939, Plaut<sup>8</sup>, in reviewing the literature, was able to collect only nine cases of carcinoid of the stomach to which he added one of his own. In the same year the tumor was observed on three additional occasions, once by Bailey<sup>9</sup> and twice by Porter and Whelan. In 1942, Lemmer<sup>10</sup> added another case bringing the total to fourteen.

In 1933, Raiford<sup>11</sup> reported the first clinical case of carcinoid tumor of the stomach. The patient was a male, fifty-five years of age with indigestion for ten months and fifteen pounds weight loss. Upon exploratory laparotomy metastases to the lymph nodes and liver were found to be present. This patient died a few days after operation.

In 1935, Pettinari<sup>12</sup> reported the first successful removal of a carcinoid tumor of the stomach. His patient was a male, age forty-seven years, who had complete pyloric obstruction.

Entwisle<sup>13</sup>, in 1937, successfully removed multiple carcinoid tumors from the stomach of a young woman, twenty-five years of age. She complained of moderately severe abdominal pain accompanied by nausea, vomiting and massive hematemesis. Roentgen examination showed punched out areas suggestive of polyposis. At operation six firm tumors of the gastric wall were excised and the patient was completely relieved of symptoms.

In 1937, Walley<sup>14</sup> examined gastroscopically a male, age forty-one years, who had persistent epigastric pain. A tumor was found and successfully removed, but symptoms were not relieved.

The patient observed by Lemmer in 1942 was a white female, age forty-four years, who thirteen years previously had had a gastroenterostomy performed for recurrent upper abdominal pain, melena and hematemesis. These symptoms persisted after the operation. Roentgenologic examination showed normally functioning posterior gastroenterostomy with no evidence of a lesion in the stomach. At exploratory laparotomy a tumor 6 cm. in diameter was found adherent to the stomach in the region of the cardia. A smaller tumor 1 cm. in diameter appeared within the gastric wall and opposite it was a healed ulcer. Gastric resection completely relieved the patient's symptoms. By personal correspondence it was learned that this patient was living and well as late as May, 1945.

#### CASE REPORT

C. B., a forty-six year old negro porter, was admitted to Jefferson Hospital with the chief complaint of epigastric fullness, anorexia and weakness which had become progressively severe over the past eight months. There had been a thirty-five pound weight loss during the past three months. There was no hematemesis, bloody or tarry stools, or diarrhea.

Physical examination revealed a well developed male, seventy inches in height and weighing 132 pounds. Aside from obvious weight loss and weakness there were no significant abnormal findings.

*Laboratory findings:* Blood count, Hb 71 per cent, RBC 3,600,000, WBC 8,000, Color index .98, normal differential; Urinalysis—normal; Wassermann and Kahn—plus 4; Van den Bergh—negative direct; Serum bilirubin—0.3 mg. per cent, Brom-sulfalein test—all dye removed; B.U.N.—9.8 mg. per cent; Urea clearance—120 per cent; Plasma proteins—5.5 gm., albumin, 3.6 gm., globulin, 1.9 gm.; Electrocardiogram—normal; Gastric analysis, free acid—0, total acid—15; Stool—Benzidine test for occult blood repeatedly positive; Sigmoidoscopy—negative for 25 cm. except for pedunculated lipoma on right buttock, and internal hemorrhoids.

Roentgenologic examination of chest, spine and long bones was normal. The radiologist's report of the gastrointestinal examination was as follows: The opaque mixture passes readily through the esophagus into the stomach. The stomach is average in position and shows a smooth rounded circumscribed filling defect in the

body which measures approximately 4.0 cm. in diameter. The mucosal folds diverge around the translucent shadow seen in the barium mixture. Although this sharply demarcated filling defect has all the signs of a benign tumor, we cannot definitely rule out the presence of malignancy. Although there is no evidence of any pedicle, the most likely diagnosis is a benign polyp. There is no gastric residue at the end of six hours and the head of the barium column is at the splenic flexure. *Impression:* Neoplasm in the body of the stomach, probably benign (Fig. 1).

*Gastroscopic examination:* The gastroscope was passed without difficulty into the lower stomach. A large tumor mass 3.0 to 4.0 cm. in diameter was noted on the



FIG. 1. ROENTGENOGRAPHIC APPEARANCE OF TUMOR

anterior wall; the surface appeared greyish white and somewhat necrotic. Surrounding the mass a number of sessile, polypoid, carmine-red, projections of mucosa were seen. No abnormalities were noted in the antrum or cardia of the stomach. *Impression:* (1) Benign tumor undergoing malignant change; (2) Gumma of stomach (Fig. 2).

Because of a history of a penile lesion twenty-seven years ago, a strongly positive Wassermann at present and the unusual gastroscopic appearance of the tumor, the possibility of the lesion being a gumma was entertained. A course of anti-leucic therapy consisting of ten grains of potassium iodide three times daily and 0.04 gm. mapharsen every other day for five doses was given, but no significant change in the tumor could be recognized by gastroscopic or roentgen examination. It was there-

fore concluded that we were dealing with a benign tumor which was probably undergoing malignant change and surgical treatment was indicated.

On October 2, 1947, operation revealed a large tumor involving the anterior wall of the pars media of the stomach. Many of the surrounding lymph nodes were enlarged and appeared to be involved by the tumor. Therefore, a total gastrectomy, splenectomy and omentectomy were performed. The patient's course was stormy for ten days following operation due to the development of pulmonary atelectasis and paroxysmal auricular tachycardia. Both conditions, however, responded to treatment and convalescence progressed thereafter uninterruptedly. The patient con-



FIG. 2. GASTROSCOPIC APPEARANCE OF TUMOR

tinued to improve following discharge from the hospital. At present, seventeen months following the operation, he is free of symptoms, has gained ten pounds and is carrying on his former duties as a porter.

*Pathological report:* A fungating, ulcerating tumor projected into the lumen of the stomach from the lesser curvature in the area of the pars media. The mass measured 11 x 8 cm. The proximal end, beginning 7.5 cm. from the cardia, sloped gradually from the mucosal surface, while the distal end, beginning 5 cm. from the pylorus, rose abruptly to a height of 4 cm. The proximal half of the tumor was reddish-tan, ulcerated and covered with patches of gray, necrotic debris. The base was deeply ulcerated and indurated. The distal half, which comprised the bulk of the tumor, was yellowish-tan, nodular and contained several shallow ulcers filled with gray, necrotic material. The largest of the nodules measured 3.5 cm. in diameter. Num-

erous large, bright red rugae passed up to the edge of the tumor, especially on the proximal side (Fig. 3).

The cut surface of the lesion was composed of dense, grayish-tan tissue with numer-



FIG. 3. GROSS APPEARANCE OF TUMOR IN RESECTED STOMACH

ous yellowish-gray areas that formed small whorls or irregular masses measuring up to 1 cm. in diameter. The growth involved all layers of the stomach. Directly opposite the tumor, the serosa was depressed for an area measuring 3 cm. in diameter. This area was bright red, firm, and adherent to the tumor.

Six lymph nodes were palpable in the gastro-hepatic mesentery along the lesser curvature of the stomach and four in the greater omentum. The largest of these measured 1.5 cm. in diameter. They were firm, grayish-tan, and of normal shape. The cut surface was homogeneously pinkish-tan, moist and firm.

Histologic examination of sections of the stomach revealed a normal mucosal pattern that was interrupted in the center by a mass of neoplastic cells which extended through all layers. An ulcer located on the free surface contained fibrin, erythrocytes, lymphocytes, plasma cells, and eosinophiles. Most of the tumor cells re-



FIG. 4. SECTION SHOWING THE CARCINOID (ARGENTAFFINE) TYPE OF TUMOR

sembled cells of a carcinoid, and were arranged into round or oval masses separated by a small amount of loose connective tissue. The centers of the larger masses were necrotic. The cells were remarkably uniform in size, shape, and staining qualities. An occasional mitotic figure was seen. Most of the nuclei were deeply stained, round or oval but a few were vesicular in appearance. The cytoplasm was pale, somewhat granular and moderate in amount (Fig. 4).

In several sections, however, the cells were anaplastic in appearance and did not resemble carcinoid. They were arranged in clusters and were quite variable in size, shape and staining qualities. The nuclei were proportionately larger and more vesicular. Mitoses were more common. Lymphocytes, eosinophiles, and plasma cells were scattered through an abundant dense stroma. Clumps of tumor cells were seen within many of the vascular channels (Fig. 5).



Sections of the tumor, stained by Foot's modification of the ammoniacal silver staining technique, showed numerous brown argentaffine granules within the cells.

Metastasis was evident in five out of eleven sections of lymph nodes. The majority of the secondary foci were of a bizarre type. The cells were arranged in cords or irregular, solid masses which blended with the normal lymphoid tissue. The cords of cells appeared as long chains of small, gland-like structures with a single layer of cells separated by a thin connective tissue stroma. The cells revealed indis-

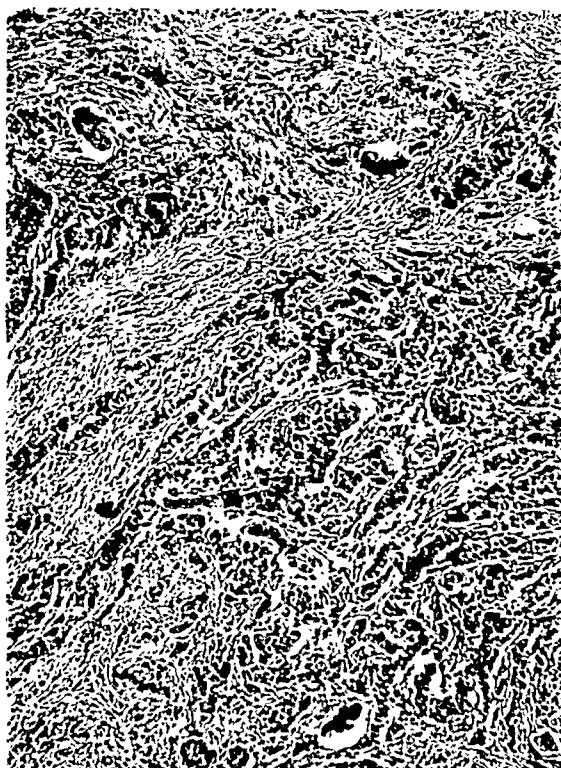


FIG. 5. SECTION SHOWING THE MALIGNANT PORTION OF THE TUMOR. NOTE THE MASSES OF NEOPLASTIC CELLS WITHIN VASCULAR CHANNELS

tinct borders, a scanty amount of cytoplasm and round or irregular darkly staining nuclei. Occasionally tumor cells were found within lymphatic channels. In only one section of lymph nodes did the neoplastic cells suggest a carcinoid tumor similar to that observed in the stomach.

Both the gross and histological examination of the spleen were non-contributory.

The pathological diagnosis was polypoid carcinoma of the stomach of the carcinoid (argentaffine) type with metastasis to the regional lymph nodes.

#### DISCUSSION

This patient represents the sixth in the group with carcinoid tumor of the stomach in whom symptoms and signs led to operation and diagnosis. In this

group there were two females and four males; the ages of these patients ranged from the second to the fifth decade. The symptoms included epigastric pain anorexia, vomiting, hematemesis, melena and weight loss. (In two patients the tumors were multiple.)

The diagnosis of these tumors on the basis of history and physical examination is practically impossible. Roentgenologic and gastroscopic examination are the best means of determining the presence, location and extent of the lesion, as well as the presence of ulceration and bleeding, but its differential diagnosis depends on histological study following operation.

The treatment of these tumors is always surgical, because, if not removed, they ultimately become malignant. When these tumors undergo malignant change they metastasize slowly, and therefore the prognosis is much more favorable than in carcinoma of the stomach.

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## MALIGNANT GASTRIC ULCER IN AN ACROMEGALIC

### A CASE REPORT

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This report concerns a case of malignant gastric ulcer in an acromegalic which presented unique gastrointestinal, neurological, endocrinological and surgical problems preoperatively but which was successfully treated by a high subtotal gastrectomy.

### CASE REPORT

§ 175819—A white male, aged 53, was admitted to the Graduate Hospital on July 9, 1946 because of "pain in the stomach." He first experienced this burning, epigastric pain several months previously following the ingestion of wine. He was nauseated and vomited. He felt weak and passed a large black bowel movement. Two weeks later the pain returned and was relieved by several ounces of whiskey or milk. He had lost 20 pounds of weight in 6 months.

The physical examination revealed a blood pressure of 160/90 and a temperature of 99 degrees. His face and hands were those of an acromegalic. The tongue was large and thick and the voice coarse. There was slight epigastric tenderness.

The laboratory examinations revealed a microcytic, hypochromic anemia. The sedimentation rate (Westergren) was 50 mm per hour. The white blood cell count and differential, blood sugar and urea nitrogen, serum proteins, calcium, phosphorous, alkaline phosphatase, bromsulfathalein, van den Bergh, urine urobilinogen, and cephalin flocculation were within normal limits. The serological tests for syphilis were negative. On July 12, 1946 roentgen examination of the stomach revealed a large penetrating ulcer arising from the posterior aspect of the lesser curvature (Fig. 1). The duodenal cap was deformed suggesting previous ulceration. Roentgenogram of the skull showed a sella turcica of seventeen mm in the antero-posterior diameter and fourteen mm in the vertical diameter as well as increased thickness in the bones of the skull. Gastric analysis showed a fasting residuum of 240 cc and a peak acid of 55 units free and 76 units total at 60 minutes.

The patient was placed on an hourly milk regimen and had stomach aspirations morning and night. He became totally asymptomatic and roentgenograms taken seventeen days after the first series showed marked healing of the gastric ulcer and normal emptying of the stomach. Gastroscopy showed no evidence of malignancy but marked hypertrophic gastritis was reported. Roentgenograms taken two weeks following the second examination showed no further healing of the ulcer. A subtotal gastrectomy was considered but abandoned because of the acromegaly and the hypertrophic gastritis. The patient was discharged August 28, 1946 on a strict medical regimen and was followed in the out patient department.

Six weeks following discharge the epigastric pain returned and he was readmitted to the hospital. The physical examination and laboratory studies were essentially the same as on the previous admission. Roentgenograms of the stomach showed a gastric ulcer of the same depth and in the same position as that of the original examination. The endocrinologists and neurologists rated the patient a poor surgical risk and advised against surgery unless "an abdominal accident was imminent." He was placed again on an hourly milk regimen and became asymptomatic. However, his

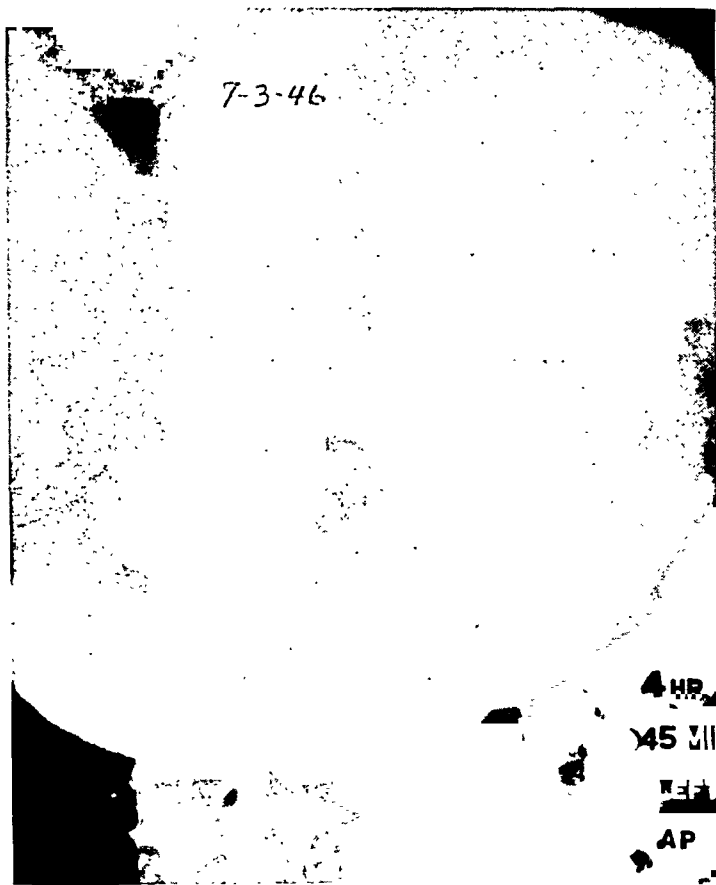


FIG. 1. ROENTGENOGRAM OF STOMACH TAKEN ON JULY 3, 1946 AT 4 HOURS AND 45 MINUTES SHOWING THE LARGE PENETRATING LESSER CURVATURE ULCER

serum proteins showed a steady decline to serum albumin 2.72 gm per cent and serum globulin 2.24 gm per cent.

The impossibility of keeping this man symptom free on a medical regimen was recognized and a high subtotal gastrectomy was recommended. He was prepared as follows: 5 per cent Amigen 1000 cc. daily for ten days preoperatively, normal human serum albumin 25 gm daily for three days preoperatively, 500 cc whole blood on the day before operation; and for three weeks preoperatively he received daily, by mouth, thyroxin 0.2 mgm and calcium glycono-phosphate grains 10 and every third day, intramuscularly, testosterone propionate 25 mgm.

On December 23, 1946 a subtotal gastric resection of four-fifths of the stomach was performed. No difficulty was encountered and the patient withstood the operative procedure very well. The microscopic diagnosis of the lesion was "adeno-carcinoma, stomach, ulcerating."

The postoperative course was uneventful. He was last studied fifteen months following resection. All laboratory studies including a complete blood count, sedimentation rate, alkaline phosphatase, and serum bilirubin were normal. Roentgenograms of the chest and stomach as well as gastroscopy showed no evidence of malignancy.

#### DISCUSSION

The presence of gastric lesions necessitating gastric surgery in acromegalics is not common in our experience and we have been unable to find any paper on the subject in the literature.

The large lesser curvature ulcer was diagnosed as benign by clinicians, roentgenologists, gastroscopists and surgeons. It appeared benign grossly. The rapid, although not complete, healing of this lesion plus the evidence of a scarred duodenal cap, presumable from a healed duodenal ulcer, further strengthened the original diagnosis. Operation was not recommended at the first admission only because he was judged such a poor surgical risk by the endocrinologists and neurologists.

The patient was on a markedly limited diet for six months. His previous dietary habits were poor hence he probably had a low protein reserve and there was a marked decrease in his serum albumin preoperatively. Normal human serum albumin was used preoperatively to correct this deficit and we believe it played a major role in the success of the surgery. The postoperative course was uneventful and the wound healed rapidly. Complete laboratory studies revealed no evidence of any other coexisting endocrinological malfunction.

The only histologic section taken from this lesion was from one edge of the ulcer. Hence we do not know if the entire ulcer was involved in the malignant process or if this was a malignant change in one part of a formerly benign ulcer.

#### SUMMARY

The recurrence in an acromegalic of a large malignant gastric ulcer that apparently partially healed on medical treatment and which was successfully removed by a subtotal gastrectomy is reported.

## Editorials

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### IS THE INSULIN TEST ALWAYS THE BEST OR ONLY TEST OF THE COMPLETENESS OF A VAGOTOMY?

As every gastroenterologist and gastric surgeon knows today, after vagotomy has been performed, and especially when the patient has not promptly lost his pain, the first question to arise is "Were all the nerve fibers cut?" Usually, the test relied on to determine this is the one in which insulin is injected. Enough of the drug is given to reduce the person's blood sugar level to approximately 50 mg. per 100 cc., and with this, if any vagus fibers remain, there should be a rise in gastric acidity.

Before going further, a few facts should be stressed. Since this reaction of the gastric mucosa depends on hypoglycemia and not on the insulin itself, a false reaction might easily be due to a failure to secure an adequate drop in the level of blood sugar. In some cases, also, the secretory reaction of the stomach is so light that it is hard to say if it is significant. It is possible, also, that shortly after an operation on the stomach the gastric mucosa is shocked and not functioning well. Furthermore, as Paulson and Gladsden<sup>1</sup> (p. 118) have remarked, when the stomach is emptying badly it is hard to get a clean sample of juice that can be titrated well, and as Johns and Grose<sup>2</sup> (p. 99) and others have pointed out, after gastroenterostomy or subtotal resection there is so much regurgitation into the stomach of intestinal contents that a moderate upsurge in gastric secretion can easily be obscured. Another possibility is that after a vagotomy in which some fibers escaped section there is a time during which they are so shocked as not to work well. During this period the result of an insulin test might well be negative, whereas later, when the fibers have recovered some function, it might be positive. Whatever the explanation may be, some surgeons have noted that a negative result from an insulin test obtained shortly after the operation changed later to a positive one.

There is another possibility, suggested by Moore and his associates and Levin, Kirsner and Palmer, and that is that some persons might give a false negative reaction to insulin after operation because their gastric reaction to hypoglycemia was weak before the operation.

As one would expect, for some time these puzzling results have been disturbing gastric surgeons and have been causing some of them to lose confidence in the test or at least in its interpretation. One of the worst puzzles has arisen in the fact that in some cases the result of the test has been positive, indicating the presence of intact vagal fibers, in spite of the presence of marked gastric stasis, lowered acidity, loss of ulcer pain, and perhaps the coming of diarrhea,

all suggesting that the vagotomy was complete. Curious puzzles in the after-results of vagotomy have been reported by most writers on the subject. Thus Johns and Grose<sup>2</sup> (p. 102) remarked that there is often no relation between the postvagotomy loss of motor activity and the loss of secretory activity. As they say (p. 100), in 3 patients who had no gastric response to insulin there was absolutely no weakening in the motor activity of the stomach. On the other hand, Bockus<sup>3</sup> had a man who after vagotomy showed a tremendous hyperacidity with a long-lasting paralysis of the gastric muscle. Paulson and Gladsden<sup>1</sup> pointed out that the secretory volume, at first greatly lowered by vagotomy, can go back up even when the insulin test, repeatedly performed, shows no sign of intact vagus nerves.

In the experience of Walters and his associates<sup>4-6</sup> the percentage of good results, as shown principally by loss of ulcer pain, was actually higher in patients with a positive reaction than in those with a negative reaction, which is just the reverse of what one would expect. Furthermore, a slowing of motility, resulting in gastric stasis, occurred just as often with a positive reaction as a negative one. A large reduction of acidity occurred in 69 per cent of the cases in which the reaction was negative and in 93 per cent of the cases in which it was positive. At the 1947 meeting of the American Gastroenterological Association, Colp, and Moore and his associates commented on puzzling experiences of this type. Johns and Grose<sup>2</sup> (p. 100) noted one case in which, in spite of a complete transthoracic vagotomy and much gastric stasis, the ulcer came back and had to be operated on again. On the other hand, a patient who had a positive reaction to the insulin test and no gastric stasis got a spectacular cure. See also Paulson and Gladsden<sup>1</sup>.

The question naturally arises after vagotomy, does a positive insulin test always mean that some vagus fibers were left? A possibility in some cases is that enough fibers were left uncut to give a positive reaction, but not enough to maintain good tonus and normal acidity in the stomach.

One point that appears to have been lost sight of in all the discussion is that there would seem to be no valid reason why the surgeon should choose to depend on only one physiologic test to satisfy him that a particular vagotomy was complete. Why depend only on the insulin test, good though it may be? Would it not be just as good physiologic practice to note if, after a vagotomy, the stomach is flaccid, dilated, slow to empty and has a low gastric acidity, a small night secretion, and perhaps a much lessened secretory reaction to emotion; also to note if the patient has diarrhea, or has suddenly lost his ulcer pain? Many physiologists might even prefer to accept these strong evidences of a big change in function.

In those few cases in which only vagotomy is performed, some physicians and surgeons might be inclined to accept a prompt and permanent healing of the ulcer as a good sign of a complete section of the nerves, and this even when

they remember that the insulin test was never proposed as an index of the clinical efficiency of a vagotomy. Actually there are many instances of a simple vagotomy without gastroenterostomy or resection in which the ulcer healed beautifully with a positive reaction to the insulin test and failed to heal with a negative reaction. As everyone should know, the insulin test has only one function and that is to determine how the gastric mucosa secretes when excited through the vagi by hypoglycemia. Actually, in the case of simple vagotomy, without gastroenterostomy or subtotal gastric resection, a prompt loss of ulcer pain and a subsequent good healing of the ulcer must always suggest that the vagus nerves were well cut, or at least cut well enough so as to get some physiologic effect. There would seem to be no good reason why this fact of spectacular healing should not be accepted in evidence together with the other signs, even though, as already pointed out, there are strange puzzling cases being reported. Probably all the several signs of a good vagotomy should be used and considered, as has been advised by Paulson and Gladsden (p. 120).

For half a century physiologists have puzzled over the fact that after an attempt at vagotomy, a few remaining fibers from one nerve will often appear to carry out all the functions of the two intact nerves. Surgeons can now do physiologists a service by making a particularly careful record and report of those curious cases in which, after vagotomy, some signs of lost vagal action appear, while others do not. Out of such a study may come helpful information. The human tendency is for us physicians to close our eyes to such cases and exclude mention of them from our papers when, actually, we should welcome these opportunities that are given us to study and learn. From such studies we might soon learn which are the best criteria of a complete vagotomy or of a vagotomy complete enough to ensure a good clinical result.

In trying to explain the persistence of a positive reaction to the insulin test after what looked like a complete vagotomy, some authorities have quoted Iwama<sup>7</sup>, who claimed that a few cholinergic fibers from the vagus nerves cross over in the neck and go down into the abdomen by way of the splanchnic nerves. Unfortunately for this argument, McSwiney and Spurrell<sup>8</sup>, 1933; Rasmussen and Duncan<sup>9</sup>, 1926; Duncan<sup>10</sup>, 1928; and Kiss<sup>11</sup>, 1932, could not confirm this. Malmejac and Donnet<sup>12</sup>, 1940, claimed that certain cholinergic nerves pass from the thoracic segments of the spinal cord to the stomach by way of the celiac plexus, but this observation will also have to be confirmed before it can be fully accepted. A simpler explanation is that some of the vagus fibers dip down into the substance of the esophageal muscle and run through it, well hidden from the surgeon who is trying to get at them. There is some evidence for this view. (Abbott 1947<sup>13</sup>)

Today one finds some men making two claims which, to a logician, would seem incompatible: one is that in a considerable percentage of vagotomies the nerves were not well cut, and the other is that in all but a few cases vagotomies,



complete and incomplete—as indicated by results of insulin tests—have resulted in a satisfactory cure of the ulcer. Some thought will have to be given to this paradox. With these ideas goes the one sometimes expressed of late that when a vagotomy fails to give a satisfactory result the reason is that it was not complete. As every historian knows, this sort of statement has been made to explain away the occasional failures that have dogged almost every therapeutic effort ever made by medical men, and hence it should be feared and avoided on principle. A moment's thought will show that in the case of vagotomy this is a poor argument. As Ruffin recently pointed out, many of the patients who, after vagotomy have had the most unsatisfactory result, are those in whom the paralysis of gastric motility was so pronounced as to be very troublesome. As Johns and Grose<sup>2</sup> (p. 100) also said, "Of the unsatisfactory cases, 5 have shown persistent gastric retention and dilation." Appleby's<sup>4</sup> (1948) experience also was that the side effects of vagotomy added much to the discomforts of convalescence from subtotal gastric resections.

Doubtless, in many cases, the resident surgeons who have had to struggle with the problem of getting a patient's stomach to empty again wished devoutly that the vagotomy had not been quite so complete! It would have been no comfort to either them or the patient to say that the result of the insulin test was positive! Certainly, with vagotomy, it would seem the part of wisdom never to blame a poor result on incomplete section of the nerves, if the stomach has become markedly atonic and markedly subacid, or if a temporary troublesome diarrhea has developed.

Always investigators in all fields will do well to remember Darwin's answer when someone asked him to what he ascribed his great success. He said the all-important thing had been never to forget or evade or explain away lightly an objection to his theory. The minute he heard of one he always made note of it so that he would not conveniently forget and ignore it. Always he grappled honestly with the difficulty, and usually, when he came to understand it, it proved to throw helpful light on his theory and its workings.

W. C. A.

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## INHIBITION OF THE MULTIPLICATION OF THE VIRUS OF MUMPS BY A POLYSACCHARIDE

In the October, 1947 number of the Proceedings of the Society for Experimental Biology and Medicine, Harold Ginsberg, Walter Goebel and Frank Horsfall, from the laboratories of the Rockefeller Institute, reported a most interesting observation, and one which may mean much for the future of the human race. Previously, Horsfall and McCarty (1947) reported that polysaccharides derived from various sources inhibit the multiplication of the virus of the pneumonia of mice. Now it has been found that the polysaccharide obtained from the capsule of the type B Friedländer bacillus is an effective restrainer of multiplication of the virus of mumps.

It is possible that more knowledge as to the chemical composition of this sugar and the way in which it stops the growth of a virus will give so much information about the chemistry of viruses that means can be found for turning the tide of battle against them. This may be an opening wedge.

W. C. A.

## Comments

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### INTERESTING COMMENTS ON VAGOTOMY BY A CANADIAN SURGEON\*

Dr. Lyon H. Appleby, of Vancouver, recently reported his experiences with 66 cases of vagotomy. He said "Of the 66 vagotomies, many results have been almost miraculous; many have been decidedly good, a few have given and still give concern, a few have been disastrous. Accustomed through the years to the smooth convalescence of gastrectomies I am at least able to say that these 66 vagotomies have given me more postoperative care and worries, resulted in more work on the part of the postoperative staff than any other 66 of my most complex gastric resections. I believe that I have met with all the postoperative troubles that any other surgeon has encountered, gastric atony, bowel and gastric distention, nausea, hiccoughs, vomiting, diarrhoea and late obstruction.

"Post-vagotomy diarrhoea has occurred in 23 of my cases. In two of my cases severe hypoproteinaemic states developed coincident with the diarrhoea, and proved to be well nigh irreversible. Large quantities of plasma, intravenous and oral amino-acids, had to be given over several weeks, but recovery occurred with dramatic suddenness in both instances, as though a back log of tissue hypoproteinaemia had finally been overcome. . . . None of the remedies in common advocacy for post-vagotomy diarrhoea has had the slightest therapeutic effect. Urocholine proved valueless. Two of my cases who had had severe diarrhoea developed late obstruction, five months and seven months respectively. . . ."

Dr. Appleby said, "Why has vagotomy received such acclaim. . . ?" and he thinks the answer is that although with gastro-enterostomy and partial gastric resection some 90 per cent of the patients got well, the trouble is that, ". . . the 10 per cent who have not had such a desirable result . . . were in worse shape than prior to their operation. The world has been looking for something which would bring a large measure of relief to these 10 per cent of unfortunates."

Appleby stated that he has been very dissatisfied with vagotomy in addition to gastro-enterostomy done for duodenal ulcer. ". . . I have now practically abandoned the use of vagotomy for duodenal ulcer and have gone back to

\*Canadian Medical Association Journal, 59: 58-62 (July) 1948.

resection." Dr. Appleby felt that vagotomy in cases of duodenal ulcer should be reserved for those cases in which resection is inadvisable or technically too difficult, or it can be done as a helper in those cases of excessively high acid values in which the surgeon fears that there will be a recurrence.

Dr. Appleby felt that vagotomy is most helpful in cases of jejunal ulcer in which the taking-down of the gastro-enterostomy or partial gastric resection would be dangerous and difficult. He thinks such operations often leave the patient crippled and unrelieved and in greater distress than he was before. He said, "I have now operated upon 11 of these cases with the most dramatically successful results in 10." The other patient died of intestinal obstruction after great distention from intestinal atony. In the cases of the patients who survived, the pain was abolished at once and the patients have had no free gastric acidity. Dr. Appleby stated that he likes vagotomy also in cases of high gastric ulcer where operation would be difficult. He thought it would be ten years before we could really appraise the value of vagotomy.

W. C. A.

#### EVIDENCE THAT THE SMALL BOWEL IS SOMETIMES INVOLVED IN THE "MUCOUS COLITIS" SYNDROME

Every thoughtful and research-minded physician should be on the watch constantly for the type of patient who, because of some disease, accident or operation, has become a suitable subject for research (of course, with his full permission and co-operation). Some six years ago Edward S. Emory found such a patient and with his intelligent co-operation made an observation which must be of interest to every gastroenterologist. The patient was a young man who had to have an ileostomy for relief of ulcerative colitis. With it he made a satisfactory recovery and thereafter remained in good health.

For years before the coming of the ulcerative colitis the man had suffered from episodes which came every few weeks or months and lasted from twenty-four to forty-eight hours. First he would suffer from malaise, lassitude, mild headache and a feeling of intoxication and then would come a feeling of abdominal fullness with distention, cramps, and perhaps rumbling and gurgling. All of these sensations were felt in the lower half of the abdomen. The usual diagnosis made by physicians was that of an irritable colon. Another possibility could, of course, have been an atypical migraine.

The interesting point was that following the ileostomy the patient continued to have the beginnings of his old attacks but not the end symptoms. What happened was that after the malaise and feeling of intoxication the ileal discharges became much more voluminous and they kept pouring out of the stoma so frequently that the man was kept busy changing the ileostomy bag.

At this time the discharges also became more than usually irritating. Then with the subsidence of the systemic symptoms, the small bowel would drop back into its normal pattern of behavior. The lack of the distress in the lower half of the abdomen seemed to be due to the fact that the colon no longer was distended and irritated by the large amount of fluid.

Incidentally, it was of interest that in this man's case the gastrocolic reflex continued to be active in spite of the interruption in the continuity of the bowel. Eating was still quickly followed by a desire to defecate and to pass a little discharge from the rectum. Strangely, this type of colonic activity was not noted during the toxic attacks.

In the case of this man the eating of certain foods, and particularly freshly gathered vegetables, tended to increase the fluidity of the ileal contents and the frequency with which they appeared at the stoma.

Some intelligent persons who suffer from an irritable colon or the so-called mucous colitis have noticed that in some attacks they can get relief by washing out the large bowel with an enema, while others find that no amount of enema-taking will do any good. They have to wait until peristalsis, starting up in the small bowel, forces gas and perhaps irritable material down into the colon, whence it can be voided. One of the curious features of some mucous colics is that during a spell the patient feels that peristaltic waves, instead of stopping normally in the rectum, where they usually are not felt, run out to the anal ring where they cause distress. Another curious feature of mucous colics in many persons is that they follow the milder nervous strains rather than the big ones. A woman may have no attack during her mother's funeral, but a bad one when she goes out to dinner next door with old friends.

W. C. A.

### A HOPEFUL DISCOVERY IN CANCER RESEARCH

In 1946 Margaret Reed Lewis, P. P. Goland and H. A. Slovirter reported that certain acridine dyestuffs of color index number 788, when added to the diet of tumor-bearing mice, stained sarcomas and spontaneous carcinomas and retarded their growth. Out of 36 commercial dyestuffs studied at that time, 5 were found to stain tumors and retard their growth.

In March of 1948, Drs. Lewis and Goland\* reported further work with 331 acridine compounds. Two hundred and four of them stained tumor tissue, and the majority of them that did this somewhat retarded the growth of the cells. Thirty-three of the compounds reduced the size of the growth to one-eighteenth of the size encountered in untreated mice. Sixteen retarded tumor growth to such an extent that the mice remained healthy, although they did have growing

\* Lewis, Margaret R. and Goland, P. P.: In Vivo Staining and Retardation of Tumors in Mice by Acridine Compounds, *Am. J. M. Sc.*, 215: 282-289 (Mar.) 1948.

tumors much smaller than those they would have had if they had not been given the drug. Actually, therefore, none of the drugs were curative; they only slowed the rate of multiplication of the tumor cells.

The majority of the 9-amino acridines that stained tumor tissue and retarded its growth show dialkyl-amino-alkyl-amino chains in the 9-position.

W. C. A.

### THE CONSTANTLY IMPROVING SITUATION AS REGARDS LONGEVITY

Everyone interested in longevity should read the most interesting statistical bulletin published by the Metropolitan Life Insurance Company for October, 1947. There it is pointed out that in the early Bronze Age, about 1700 B.C., the average length of life was about eighteen years. About the time of Christ, the average length of life as indicated by the ages at death noted on mummy cases, was twenty-two years. In the middle ages it ranged about thirty-five years. In the United States, around 1900, it was 49.2 years and in 1945 it was 65.8 years. At present it must be at least 70 years.

During this last year there has been a marked drop in the death rates among the Metropolitan industrial policyholders. The death rate for tuberculosis has been going down rapidly. That for appendicitis has dropped to a new low, and with the help of the new antibacterial drugs the death rate for pneumonia has gone way down. Pneumonia and influenza together now account for less than 4 per cent of the total mortality; ten years ago these diseases were outranked only by heart disease and cancer, and were responsible for 10 per cent of all deaths.

It is found now that the death rate among American physicians is practically the same as that of the population as a whole. However, among the physicians there is an abnormally high incidence of diseases of the heart and coronary arteries. These account for 40.7 per cent of the deaths. Next in rank come intracranial lesions of vascular origin which account for 10.8 per cent. Then comes cancer with almost 10 per cent, nephritis with 6 per cent, and pneumonia and influenza with 5.5 per cent.

Curiously, compared with white men in the general population, male physicians have unusually low death rates from most infectious diseases, and this in spite of the fact that many are constantly being exposed to infections. Physicians also are less than normally subject to tuberculosis, to accidents, and to the troubles that are amenable to surgery. Physicians have only one-third the American white man's tendency to acquire syphilis. As already noted, it is when we come to a consideration of the vascular diseases that we find physicians about 20 per cent more than normally susceptible.

It is curious that physicians are one and three-fourths times more susceptible to leukemia, and this may be due to the exposure of many to roentgen rays.

It is sad to read that some 3,000 boys and men are killed accidentally each year while engaged in some outdoor sport. About 70 per cent of these deaths were accounted for by the three sports of hunting, fishing and swimming.

W. C. A.

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## Book Reviews

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LES ICTERES. *I. Pavel*. Second Edition. "CANDIDA" Anton Richter. Bucharest. 1944. pp. 189.

Pavel has long puzzled over the question of why icterus accompanies some cases of hepatitis and not others. To explain the difference he proposed a theory of infiltration and resorption. In the new edition there is a chapter on the formation of bilirubin. Already in 1942 in Rumania there was a big epidemic of icterus and this was studied carefully by Pavel. The book should be of great interest to anyone who reads French and wishes to see what has been done in this field of medicine in Rumania.

BIOLOGY OF DISEASE. *Eli Moschowitz, M.D.* Grune & Stratton, New York. 1948. pp. 221. Price \$4.50.

This is an interesting and thought-producing book which all good internists ought to read. As the writer states, when chronic disease is observed closely, one notes that many syndromes are not so sharply defined as they seem to be in textbook descriptions. Instead one disease seems to shade into or be related to another. Perhaps even the detailed differentiation that has been worked out by keen students of a disease has tended to confuse rather than to simplify the picture, and has caused the classification of some diseases to be more artificial than biologic. There are many chronic diseases, also, which go through stages of evolution from youth to old age, and it would be just as sensible to classify the earlier, the intermediate, and the final phases of the disease as separate entities as it would be to describe a tadpole and a frog as belonging to different species. Naturally, much of this confusion in the classification of diseases stems from our ignorance of the causes.

One of the most interesting things that can be done in the future is to study diseases as they appear in several members of a large family. For instance, we remember a man who suffered from pernicious anemia while his son had an acute leukemia and we remember a family in which two daughters were insane and the third died of atrophy of the adrenal glands. One wonders in such cases if it is not more than a coincidence that the two types of disease met in members of one family.

Moschowitz evidently has a remarkable knowledge of disease and of the literature on it, and he thinks philosophically about his problems, trying to find answers to many questions. Hence it is that his book is particularly delightful. It consists of a series of 24 essays, several of them on rare diseases. There is a remarkable article on periarteritis nodosa and another on the Libman-Sacks disease. In the latter article Moschowitz discussed all the various relations of this disease to other rare syndromes such as lupus erythematosus. Gastroenterologists will find much to interest them in articles on obesity, peptic ulcer, achlorhydria in relation to anemia, cardiospasm, the sprue syndrome, and psychosomatic medicine. Moschowitz points out that in many cases of cardiospasm there are psychic factors at work.



On page 167 one finds an interesting idea, that in the production of certain diseases such as exophthalmic goiter, there is first the inherited constitution; then there can be psychic strain with an exaggeration of normal autonomic functions; then the persistent presence in the body of an overdose of hormones can damage tissue in the thyroid gland, heart and liver, and finally one finds definite and permanent organic disease.

It is delightful to find someone writing on medicine not only with clinical wisdom but a philosophical point of view; one likes his ability to see the relationships between many conditions and parts of syndromes, and one sympathizes with his efforts to understand why several conditions come together sometimes in the same syndrome or in the case of the same patient or the same family. Unfortunately, in medicine today, the average physician is too busy making a living and treating patients ever to do the sort of puzzling and thinking which one finds in this book.

TECHNIC OF MEDICATION. *Austin Smith, M.D.* J. B. Lippincott Company, Philadelphia. pp. 255.

This is an excellent book by the Director of the Division of Therapy and Research, Secretary to the Council on Pharmacy and Chemistry of the American Medical Association. It contains some of the material which was published in Fantus' *General technic of medication*, which ran through three editions.

While the book was intended primarily for the medical student and intern, it is obvious that it can be of great value to physicians who want a refresher course in treatment. The book contains much valuable material which is hard to find in other places. There are so many procedures which are not likely to be taught in medical school, but which the intern and the resident learn during their years in a teaching hospital. In this book these procedures are described in detail. There is information even on such things as the care of hypodermic syringes and needles. There are chapters on writing prescriptions, on the giving of drugs by mouth, on injections of various kinds, on rectal and genito-urinary administrations, on applications to the skin, and on applications to the mucous membranes.

This would be a splendid volume to give to an intern as he comes into a hospital to take up his work. It would help him greatly.

Dr. Smith is to be congratulated on a good job well done.

THE DIGESTIVE TRACT IN ROENTGENOLOGY. *Jacob Buckstein, M.D.* J. B. Lippincott Company. Philadelphia. 1948. pp. 889.

This is an attractive book with 1030 illustrations and 659 figures. Dr. Buckstein is assistant professor of clinical medicine at Cornell University Medical College and visiting roentgenologist (Alimentary Tract Division) in Bellevue Hospital. Any man who would read this book through would get a liberal education in gastroenterology. The illustrations alone are of great value. There is so much good material in the volume that it is hard to pick out any special part for special commendation. It is a book that every gastroenterologist should have close at hand.

FAILURES IN PSYCHIATRIC TREATMENT. *Paul H. Hoch, M.D.* Grune & Stratton, New York. 1948. pp. 239.

One of the finest things that a physician or research worker can do is to write up his bad results and his failures and then if possible to show why he failed. Medical literature, filled with the overly-optimistic reports of therapeutic measures, contains too few frank reports of failures. Too often a procedure is used for a time by physicians and then when the results are found to be bad, no one says anything about them. All that happens is that the method or operation is dropped.

Too often men who have proposed a treatment come to look upon it as their beloved child who can do no wrong. They only answer to the man who reports that, in his hands, the treatment is useless or worse than useless is that he didn't select his cases properly or he didn't use the procedure strenuously enough. If it is a drug, he should have quadrupled the dose.

Whenever one sees this sort of argument one is reminded of Dr. Sangrado, in the remarkable novel "Gil Blas." Sangrado claimed that he could cure all diseases by bleeding the patient and then making him drink large quantities of water. His patients were dying right and left but whenever his attention was called to one of these bad results he always said the man wasn't bled enough and he wasn't given enough water! The possibility that his treatment could be all wrong and harmful never entered his head.

Accordingly, it is with great pleasure and gratitude that we greet this book on failures in psychiatric treatment. There are fifteen chapters written by the leaders in the field. Particularly helpful is the chapter on prefrontal lobotomy which should make every physician think twice before ordering such an operation in the case of a person who is not in bad shape. The last state of that patient might be most distressing, especially if he should wind up lazy, useless, untidy, dirty and unable to control his bladder.

Helpful also is the chapter on electric shock therapy. According to Dr. Horwitz, the failures are greatest and most consistent in the treatment of psychoneuroses. It is not likely to be of any use in the treatment of psychopathic or schizoid personalities. As he says, in persons with a reactive depression, it is possible to alleviate the depressive state, but one must not expect any fundamental change in the underlying psychoneurotic condition. The treatment has been almost completely ineffective in the cases of involutional melancholia with an agitated type of depression, or in cases of the long lasting type of depression. The most consistent failures have occurred in a group of patients with a bizarre disabling type of compulsive and obsessive symptoms which have persisted for years. Electric shock treatment is apparently of little use in the schizophrenias.

Very interesting is the chapter on the heredity of psychic troubles as shown in similar twins. In view of the present-day tendency of psychiatrists to ignore the tremendous influence of heredity in producing psychoses and neuroses it is a joy to find Dr. Kallman doing his wonderful work on hundreds of monozygotic twins.

There are other chapters on failures in attempts to treat criminals with psychotherapy and failures in the treatment of epilepsy and neuro-syphilis.

Some men may say, "But why be so discouraging?" and the answer is, in science no good ever comes from sticking one's head in the sand like an ostrich.

**ACUTE INTESTINAL OBSTRUCTION.** *Rodney Smith.* (With a Chapter on Radiological Diagnosis by Eric Samuel.) Foreword by Rupert Vaughan Hudson. The Williams & Wilkins Company, Baltimore. 1948. pp. 259. Price \$5.00.

This is an attractive volume with a great deal of practical information in regard to intestinal obstruction. It is written by the assistant surgeon to St. George's Hospital in London. Smith insists on the value of suction drainage as a routine measure in all cases of acute obstruction in the small bowel. The obstruction in itself does not kill if dehydration is corrected, but intestinal distention above the obstruction and the results of a rising intraluminal tension are serious, and suction tends to obviate them. Smith admits that in many cases of strangulated external hernia in which the patient is seen promptly, quick operation is enough. Even then, however, he thinks that the use of suction drainage is helpful. Interesting is Smith's description on page 124 of an oblique end-to-end anastomosis with 180 degrees rotation of the segments. This tends to prevent later narrowing of the lumen.

One of the best things about this well written and well planned book is that it appears to be based on the writer's own large experience.

**NON-PROJECTIVE PERSONALITY TESTS.** A Series of articles by different writers published in the Annals of the New York Academy of Sciences, vol. 46, Art. 7, pages 531-678, New York, 1948.

This is a series of articles by psychiatrists on the value of several types of personality tests that can be given to large groups of men with the idea of quickly weeding out the psychopathic persons. It appears that these tests have decided usefulness and doubtless with time they will become perfected.

**HEMORRHAGE.** A series of articles published by *Gregory Schwartzman, et al.* in the Annals of the New York Academy of Sciences, vol. 49, Art. 4, pages 483-660, 1948.

This is a splendid group of articles on the problems of hemorrhage. They will be of great interest to every hematologist and to many an internist.

# ABSTRACTS OF CURRENT LITERATURE

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## STOMACH

ANDRESEN, A. F. R. Management of gastric hemorrhage. N. Y. State J. Med., 48: 603 (Mar.) 1948

The patient should not be disturbed by excessive questioning or examination. Other sources of bleeding as nose, mouth, esophagus, and lungs should be ruled out. Hemograms are done and if the coagulation is disturbed, coagulants should be administered. Blood urea estimations are done every second day and stools are tested for occult blood. Shock is treated by rest, warmth and sedation. Large transfusions are contraindicated. Not more than 200 cc. should be given at a time. In extreme cases one may give a continuous transfusion by drop method using 6-8 liters if necessary. The patient is placed on a routine gastric hemorrhage diet consisting of: 6 oz. of a mixture of milk, cream and dextrose every 2 hours for the first 4 days, then eggs, cereals, custards, and jello gradually added until the 9th day when the ordinary ulcer diet is given. The bowels are kept open by mineral oil and retention enemas. If the bleeding has stopped by the 12th day one may do a gastric analysis, and on the 14th day a barium series. The following must be

avoided: (1) ice, externally because it increases shock, and internally because it stimulates gastric circulation; (2) parenteral fluids, and stimulants because they tend to raise the blood pressure and increase bleeding; (3) alkalies, which stimulate secretion and irritate bleeding areas; and (4) excitement or worry.

PHILIP LEVITSKY

FINKELSTEIN, C. Zur Frage der Behandlung des inoperablen Magenkrebses mit Übertragung von Magensaft gesunder Menschen. [The treatment of inoperable gastric cancer by the administration of gastric juice of healthy individuals]. Gastroenterologia, 72: 306 (1947).

Approximately 200 patients with inoperable gastric carcinoma were treated by the administration of gastric juice obtained from other individuals. The juice was obtained either from the fasting or postprandial stomach in amounts of 100 to 150 cc. and administered to the recipients by stomach tube. Usually the treatment is followed by increase in appetite and improvement in well-being. No influence on the growth of the tumor was observed. The improvement was temporary in all cases. Some

patients complained of abdominal discomfort following the administration of normal or hyperacid gastric juice.

CHARLES A. FLOOD

### BOWEL

KROOK, S. S. Intestinal suction treatment.

*Acta Chir. Scand.*, 96: 562 (June) 1948.

The Miller-Abbott tube is recommended for aspiration of small intestinal contents. There are at least two modifications, i.e. the Harris tube and the Cantor tube. The tube is inserted through the nostril like an ordinary stomach tube. There is difficulty sometimes in passing it through the pylorus; this may take hours. The tube has a double lumen, one part of which is connected to a balloon, which is inflated with 20 c.c. of air when the end of the tube is in the intestines (verified fluoroscopically). The second section of the lumen is used for suction or injection. Complications after its use are rare. However, there may be damage to the larynx with infection, and otitis media may occur in children. The principal indication for the use of the tube is paralytic ileus. If the intestines are decompressed and the fluid balance maintained, recovery occurs without operation. In the cases of mechanical obstruction, some surgeons prefer to operate first and then drain. Others feel that it is better to decompress the bowel first and then remove the obstruction. All are agreed that, in strangulation which may simulate mechanical obstruction, there is great danger in postponing operation in favor of intubation. Strangulation is usually of much more sudden onset than obstruction, particularly after gynecological operation. In strangulation the pain is continuous with periods of intensification, whereas in obstruction there are intervals of freedom from pain. Differential diagnosis is nevertheless often impossible.

PHILIP LEVITSKY

KROOK, S. S. Obstruction of the small intestine due to adhesions and bands.

*Acta Chir. Scand.*, 95: Suppl. 125 (1947).

The author, by studying a large series of cases of intestinal obstruction due to adhesions, attempts to elucidate the late prognosis and the conditions under which recur-

rences arise. The cases are divided into (1) those following acute peritoneal infection, and (2) those due to a mechanical adhesion-producing factor. Among 417 cases in the first group, the frequency of late obstruction was 4 per cent; 89 per cent of the survivors had satisfactory operative results, and 7 per cent had persistent symptoms. In the second group of 118 gynecological cases, the frequency of obstruction was less than 1 per cent; 90 per cent of the survivors were free of symptoms. In the total series following the first operation for intestinal obstruction, the risk of recurrence was 14%; a satisfactory result was obtained in 68%; 18% had persistent symptoms; and 2% died from subsequent recurrent obstruction.

In this study the frequency of recurrence did not seem to be related to age, sex, inadvertent intestinal puncture, nor to the diffuseness of adhesions at the time of the first operation. It was dependent rather upon the character and degree of the preceding pathological process. The mortality of the second operation for intestinal obstruction (9%) was lower than that (20%) of the first; the recurrence frequencies (16% and 14%) did not differ appreciably, but the incidence of persistent distress was statistically higher for the second operation (76%), than for the first (43%).

Concerning the treatment and prophylaxis of intestinal obstruction due to adhesions, the author draws the following conclusions: (1) The range of indication of the use of the Miller-Abbott tube and other non-operative measures should be broadened in repeated attacks of subobstruction and in patients who are poor surgical risks. (2) During laparotomy a careful search should be directed towards foci of chronic infection, Meckel's and other diverticuli, and dilated short-circuited loops. (3) Careful attention should be given to peritonealization. (4) Enterostomy should be avoided. (5) Where entero-anastomosis is necessary, resection should be carried out if at all possible.

DAVID A. DREILING

MÖLLER, W. Solitary neurinoma of the small intestine. *Acta Chir. Scand.*, 96: 1 (Sept.) 1947.

Neurinomas arise from nerve fibres. In the

alimentary tract they may appear in multiple form, sometimes combined with cutaneous neurofibromatosis (Von Recklinghausen), or as solitary tumors which are discussed in this report. The most common site of a solitary tumor is in the stomach, according to the 20 cases published to date. The symptoms depend on the location and site of the tumor. The most common complaint is abdominal pain due to mechanical obstruction. The tumors may be large and can sometimes be felt per abdomen or per rectum. While most tumors reported were benign, 2 have proven to be malignant, and the author is of the opinion that all neurinomas should be regarded as potentially malignant. They should be removed by resection of the segment of bowel, and not by a simple extirpation.

PHILIP LEVITSKY

BACON, H. E., AND ROWE, R. J. Primary resection for cancer of the lower bowel.

N. Y. State J. Med., 48: 607 (Mar.) 1948. Five hundred and sixty cases with cancer of the sigmoid, rectum and anus are reported. The incidence of node metastases was 36 per cent. The prominent symptoms were: bleeding in 85 per cent; increasing constipation in 54 per cent; diarrhoea in 31 per cent; "false urge," with expulsion of flatus only, in 38 per cent; incompleteness of evacuation in 42 per cent; early morning diarrhoea in 17 per cent; "pencil stools" in 5 per cent; and sensory disturbances referable to bladder in 8 per cent. Pain was present in 55 per cent of the cases. The tumor could be palpated in 77 per cent and was seen sigmoidoscopically in 89 per cent. On the average, 9.7 months had elapsed between the onset of symptoms and the examination. Of the 560 cases, 526 (90%) were operated upon. Four hundred and sixty-seven (80%) had resections, with an immediate mortality of 5.5 per cent. Many cases can be operated on with preservation of the anal sphincters—the so-called abdominoperineal sigmoidectomy. In 317 cases in whom this operation was performed the operative mortality rate was 4.7 per cent. Of 180 cases studied, 80 per cent of the tumors were at least 3 cms. above the anus and were fit subjects for this operation. This procedure is preferable to

the Miles operation, since the morbidity is less, and the rate of sexual impotence in males is only 8.3 per cent as compared to 95 per cent following the Miles procedure. The rate of 5-year cure based on all cases, after the method of Newman of the British Ministry of Health, was 52.6 per cent.

PHILIP LEVITSKY

HODGES, F. J., RUNDLES, R. W., AND HANLIN, J. Roentgenologic study of the small intestine. II. Dysfunction associated with neurologic diseases. Radiol., 49: 659 (Dec.) 1947.

This paper covers an entirely new field in roentgenology. The illustrations are of great importance. The authors studied 30 cases with diabetic neuropathy. The roentgenographic findings showed a wide range of abnormality falling under the heading of "disordered motor function." Some degree of gastric retention, prolonged barium transit through the intestinal tract, and segmentation of the barium column were fairly constant features. The caliber of the gut lumen showed considerable variation, and localized segments of dilated gut were encountered. The mucosal pattern was well preserved. However, localized coarsening, irregularity, and partial obliteration of folds were not infrequently observed. Abnormalities of the same type and degree occurred in those suffering from severe constipation as in those with chronic diarrhea. Gastric retention and delayed transit through the bowel were found in cases of diarrhea.

In pernicious anemia patients with severe symptoms, significant gastric retention was not observed; otherwise the signs of disturbed intestinal function were not unlike those encountered in diabetics with associated neuropathy. In tabes dorsalis with "gastric crises", no special pathology could be seen, but there was difference on examination during a period of nausea and vomiting, as compared with a symptom-free period.

FRANZ J. LUST

BENNETT-JONES, M. J. AND WIGGLESWORTH, G. F. Atypical Crohn's disease. A report of three cases. Brit. J. Surg., 35: 66 (July) 1948.

The first of these cases was atypical because

of the massive size of the mesenteric glands which eventually burst causing peritonitis, and the second was due to involvement of the cecum without the ileum. The third case was unique because the presenting symptom was repeated evanescent swelling of the right buttock. Due to the history of sciatica, emaciation, pyrexia and limitation of motion, the diagnosis of tuberculosis of the hip was entertained. However, at operation an inflammatory mass in the pelvis was found and shown on histological study to be typical regional ileitis.

C. WILMER WIRTS, JR.

OHNELL, H. Chronic obstipation usually a wrong diagnosis. *Gastroenterologia*, 72: 383 (1947).

In the treatment of so-called obstipation, the author uses a diet rich in fruits, vegetables, whole wheat flour and rye, to which bran may be added. In refractory cases, a water-enema or oil-enema is permitted. After the bowel defecation reflex has been reestablished for two or three weeks, the patient may, as a rule, reduce the amount of laxative foodstuffs in the diet. The patient with obstipation should abstain from laxatives. Mineral oil also should be avoided because it has been found by proctoscopic observations that this oil may irritate the intestine.

In the author's experience chronic obstipation arises from an acute obstipation, brought about by confinement to bed, and which was mismanaged with laxatives causing a laxative habit. The term, chronic obstipation, is therefore apt to be misleading.

CHARLES A. FLOOD

## LIVER AND GALL BLADDER

BORENSZTEJN, H. Homologous serum hepatitis. *Lancet*, 254: 941 (June) 1948.

This report deals with 226 cases of hepatitis, seen in a military center for the treatment of syphilis. Ten cases are excluded because these were apparently the result of arsenic intoxication. The etiologic agent was probably a virus transmitted by inadequately sterilized syringes; the average incubation period was 90 days. In 70 per cent of the patients, the presenting symptoms were pyrexia and prostration in the pre-icterus stage. Thirty per cent presented themselves

with gastrointestinal upsets. There were 40 deaths in the group, an incidence of 17.7 per cent. When the syringes were sterilized according to the technique of Preston, the number of cases diminished sharply. The author was able to transmit the disease to a rabbit by injecting blood from a fatal human case. The rabbit died from acute yellow atrophy.

PHILIP LEVITSKY

GOLDBLOOM, A. A., LIEBERSON, A., AND ROSEN, C. D. Clinical studies in jaundice. The use of sedimentation rate determinations in the convalescent stage of infectious hepatitis. *N. Y. State J. Med.*, 48: 1254 (June) 1948.

In the pre-icteric and early icteric phases of infectious hepatitis, the sedimentation rate is below 10 mm. (Wintrobe) in about 85 per cent of the cases. This is attributed to the presence of bile salts in the blood. In the first 10 days of malaria, about half of the patients have a sedimentation rate above 10 mm. The sedimentation rate goes up in the later stages of infectious hepatitis, and recovery cannot be considered complete until it returns to normal. In this respect, sedimentation rate is a more reliable indicator than the cephalin flocculation test. In 26 cases recovering from infectious hepatitis, 25 gave a raised sedimentation rate whereas only 15 gave a positive cephalin flocculation test.

PHILIP LEVITSKY

EDLUND, Y. Studies on the carbohydrate metabolism and liver protection therapy in experimental extrahepatic biliary obstruction. *Acta Chir. Scand.*, 96: Supp. 136 (1948).

The author presents an extensive review of the causes, pathology, and biochemical changes in carbohydrate metabolism following complete and incomplete experimental extrahepatic biliary obstruction in the rat. Technique, pathology, and biochemical methods are discussed in the first of the five sections of the monograph. The second part deals with the pathological changes in the liver, kidney, and skeletal musculature and with the mechanism originating hyperbilirubinemia. Parts 3 and 4 are devoted to

the causes and nature of the disturbance of carbohydrate metabolism in total biliary stasis, and the last section reports the effect of "liver protective therapy" under the experimental conditions. The conclusion is drawn that parenteral amino acids, glucose, and methionine, did not prevent or modify the liver lesion.

DAVID A. DREILING

HAINES, F. X. AND KANE, J. T. Acute torsion of the gallbladder. *Ann. Surg.*, 128: 253 (Aug.) 1948.

As of 1946 there were only 76 cases of acute torsion of the gall bladder reported in the literature. This condition can develop only when the gall bladder is free except for the attachment of the cystic duct. It is found typically in elderly, visceroptotic females. It is manifest by sudden onset of pain, later a tender palpable mass in the absence of constitutional symptoms such as jaundice, fever and increased pulse rate. The following case report was presented.

A thin, 63-year old white man was seized with severe peri-umbilical pain which persisted without radiation. The patient vomited several times. There had been no similar episodes previously. A smooth, pear-sized mass was palpable one inch above the umbilicus to the right of the midline. At operation a dark, shiny gall bladder presented itself. It was attached only at the cystic duct; the neck of the gall bladder was twisted 360 degrees.

LEMUEL C. MCGEE

GOODWIN, J. Liver function tests in cases treated with thiouracil compounds. *Brit. Med. J.*, 4566: 64 (July) 1948.

Eighty-one cases of thyrotoxicosis, under treatment with thiouracil compounds, were submitted to hepatic function tests in addition to clinical assessment of liver function at 3-6 month intervals. The tests used were serum bilirubin, thymol turbidity, Takata-Ara, alkaline phosphatase, total serum proteins and differential serum proteins. Abnormality in only one test occurred in 24 cases, and this was considered to be of doubtful significance. Eight cases showed abnormalities in two or more tests; these were interpreted as evidence of impaired hepatic

function. Two of these patients were jaundiced; one died of hepatic cirrhosis, which appeared to be related to the disease rather than to the therapy, and the other improved with further thiouracil treatment. One case, which showed no abnormalities in tests after treatment for 4 months, developed evidence of hepatic damage after a further 6 months' treatment. In the other cases, the abnormalities were diminished or unaltered by thiouracil treatment. It is concluded that, in many cases, thiouracil drugs improve or do not affect liver function, but that in some cases deterioration may occur under treatment. This should not constitute a contraindication to thiouracil therapy, since such deterioration may be due to the disease rather than to the thiouracil.

JOSEPH B. KIRSNER

LINDER, H. K., BRUGER, M., AND GREENE, C. H. Comparative studies with some 'newer tests for hepatic dysfunction. *N. Y. State J. Med.*, 48: 1371 (June) 1948.

The three tests in common usage to-day, indicative of acute parenchymal damage of the liver, are the cephalin-cholesterol flocculation test of Hanger, the colloidal gold reaction, and the thymol turbidity test of MacLagen. These tests were carried out in 169 individuals. All tests on 9 controls were negative. Nine cases of infectious jaundice were investigated, and in the majority the tests were positive. Thirty-two patients with cirrhosis of the liver were studied; the majority of these were jaundiced. In 21 of these patients, all 3 tests were positive; in 7, one or more tests were positive; but in 4, all the tests were negative. In 13 cases of obstructive jaundice, the tests were negative in all but 3 cases. It was felt that the obstruction in these 3 patients had already produced liver damage. The results were variable in secondary carcinoma of the liver (8 cases). One may get positive results in extrinsic conditions, such as sarcoidosis, lymphosarcoma, and lymphatic leukemia, where there is secondary hepatomegaly. Passive congestion of the liver secondary to the heart (10 cases) gave normal readings. Malaria may give false positive test-results. The 3 tests were normal in such unrelated conditions as chronic glomerulonephritis,



asthma, acute infections, and Hodgkin's disease. These tests are of great value in the differential diagnosis of types of jaundice. The cephalin-cholesterol flocculation and the thymol turbidity tests are relatively simple to perform and should become office procedures.

PHILIP LEVITSKY

TROESCH-PAILLARD, S. Über die biliare Leberzirrhose [Biliary cirrhosis of the liver]. *Gastroenterologia*, 72: 96 (1947). A series of 17 proven cases of biliary cirrhosis was analyzed to determine the points of difference between this form of cirrhosis and Laennec's cirrhosis in regard to clinical findings. In the majority of cases, there was associated disease of the extrahepatic biliary tract. The clinical course was characterized by persistent or recurring jaundice, bouts of pyrexia, and attacks of right upper quadrant pain. Enlargement of the liver and spleen were usually present. Low-grade fever was frequent and there was a leukocytosis with a shift to the left. An increase in the total blood cholesterol was usually found with a decrease in the cholesterol fraction. The changes in blood chemistry were otherwise similar to those commonly found in Laennec's cirrhosis.

CHARLES A. FLOOD

KUNKEL, H. G., LABBY, D. H., AHRENS, E. H., JR., SHANK, R. E., AND HOAGLAND C. L. The use of concentrated human serum albumin in the treatment of cirrhosis of the liver. *J. Clin. Invest.*, 27: 305 (May-part 1) 1948.

At the hospital of the Rockefeller Institute for Medical Research, concentrated human serum albumin—in standard units, each containing 25 g. albumin (the amount derived from 500 cc. plasma)—was used in treating 17 patients with advanced degrees of hepatic cirrhosis. Follow-up observations were continued as long as 28 months after completion of the therapy. Therapeutic effectiveness was evaluated by the influence of the injected albumin on the ability of the liver to resume normal synthesis of albumin. This treatment was found to carry seriously ill patients through the early critical period of their disease, until

such time as dietary and liver extract therapy had an opportunity to take effect.

Fourteen of 15 patients with ascites lost their fluid following therapy. The amount of albumin used ranged from 4 to 80 units per patient. Patients with particularly severe liver disease and very low plasma albumin levels following infectious hepatitis responded most readily. Cases with alcoholic and nutritional cirrhosis and a short period of ascites responded to relatively small doses of albumin. Permanently beneficial results were obtained in 6 of 7 patients with nutritional type of cirrhosis. Patients with postnecrotic cirrhosis, after infectious hepatitis and biliary cirrhosis, showed only temporary response. Patients, with marked evidence of portal obstruction, a high anti-diuretic titre in the urine, or long standing ascites, proved very resistant to this therapy.

SAM OVERSTREET

## PANCREAS

AUFDERMAUR, M. Über Pancreasnekrosen als Folge generalisierter Arteritis. [Pancreatic necrosis resulting from generalized arteritis.] *Gastroenterologia*, 72: 81 (1947).

Ten cases are reported in which there was pancreatic necrosis or focal atrophy of the pancreas due to an obstructive arteritis. In 9 of the 10 patients, there was associated malignant nephrosclerosis; one patient had subacute glomerular nephritis. Arterial disease was present in the coronary, adrenal, splenic and cerebral arteries in some cases. The pancreatic necrosis was seldom important clinically and was overshadowed by the symptoms of renal disease. Focal infection, especially chronic tonsillitis, was found in some cases and is suggested as a possible cause of the obstructive arteritis.

CHARLES A. FLOOD

HJORTH, E. Contributions to the knowledge of pancreatic reflux as an etiologic factor in chronic affections of the gall bladder. An experimental study. *Acta Chir. Scand.*, 96: Supp. 134 (1947).

The author reviews the literature of pancreatic reflux and presents anatomical, physicochemical, and experimental investigations of his own to support pancreatic reflux as an

etiological factor in the production of pancreatic disease. The anatomical studies are based upon 100 autopsy dissections and 430 operative cholangiograms. Possible communication of the common bile duct and the pancreatic duct exists in about 86 per cent of the cases and this communication was found to be 3 times more common in females than in males. The author concludes that the latter fact may account for the preponderance of biliary disease in women. The physicochemical studies showed that bile containing pancreatic ferments was present in the gall bladder in 15 out of 100 cholecystectomized patients. The concentration of these ferments and other factors preclude their extrapancreatic origin. Nine of the 15 cases had cholangiograms; in 6 of these there was visualization of the pancreatic duct.

Experimentally, the author studied the effect of injecting active and inactivated trypsin into the gall bladder of rabbits following occlusion of the cystic duct. The inactivated enzyme caused no change in the gall bladder wall, but active trypsin produced the pathological picture of chronic cholecystitis associated in some instances with the formation of calculi.

The physicochemical aspects of the pancreatic reflux theory are discussed. The author concludes that acceptance of this theory would imply a deeper understanding of the intimate relationship between gastrointestinal disturbances, pancreatitis, and biliary tract disease.

DAVID A. DREILING

WERMEL, E. M. AND KACHAROVA, E. A. The role of the basal-granular cells of the mucosa of the small intestine in the production of secretin. *Anat. Rec.*, 101: 595 (Aug.) 1948.

The basal-granular cells are constant cell elements in the epithelium of the mucosa of the duodenum and appendix of mammals. These cells are often called argentophilic because they take a silver stain. "Basal-granular" cells most aptly characterizes their morphology. These cells are cone-shaped, with the base turned towards the basal membrane; they contain small granules that accumulate mostly in the basal part of the cell.

The functional significance of these basal-granular cells has remained obscure. The authors consider it very probable that it is these cells that secrete secretin for two reasons: (1) The basal distribution of the secretory granules and their proximity to the underlying blood capillaries are typical of cells producing hormones (incretins), and (2) a remarkable parallelism is observed in the distribution of the basal-granular cells and the amount of secretin in them. In guinea pigs and white rats a piece of intestinal mucosa just beyond the pylorus was fixed, stained and studied. The number of basal-granular cells in the glands of Lieberkuhn were noted carefully. Following the introduction of hydrochloric acid into the pyloric area of other animals, morphologic studies revealed a diminution in the number of visible basal-granular cells. Interestingly, in the white rat a rebound phenomenon was noted, namely an increase in the number of basal-granular cells, some time subsequent to the introduction of the hydrochloric acid. The hydrochloric acid results not only in the discharge of secretin, but also acts as a stimulus for regeneration of the granular material.

FRANK NEUWELT

WERMEL, E. M. AND KACHAROVA, E. A. A study of the basal-granular cells of the mucosa during regenerative processes in the pancreas. *Anat. Rec.*, 101: 605 (Aug.) 1948.

The authors believe that secretin is produced in the basal-granular cells of the intestine and that this hormone stimulates or excites the endocrine part of the pancreas (the insular apparatus). The authors state that evidently the hormones of the mucosa exert their influence by one of several means: (1) induce discharge of insulin (insulinocentric effect), (2) stimulate the accumulation of secretin (insulinotropic effect), or (3) activate the genesis of new insular tissue (insulogenic effect). Rats were used as the experimental animal and were subjected to three types of operation: partial pancreatectomy, one-sided adrenalectomy, and laparotomy with traumatization of the omentum. The results of histological examinations of the duodenum following pancreatectomy showed a marked and persistent increase of the

basal-granular cells of the mucosa. The "alarm reaction," caused by epinephrectomy, resulted in a temporary increase of the basal-granular cells. These cells also increased markedly as a result of acute inflammation and traumatization of the omentum. The authors conclude that these experiments make plausible the hypothesis that a correlation exists between the number of basal-granular cells in the intestine and the activity of the  $\beta$  cells of the Island of Langerhans. They believe that the basal-granular cells secrete a hormone which stimulates the island cells of the pancreas.

FRANK NEUWELT

### ULCER

APPLEBY, L. H. An assessment of the results of vagotomy. *Can. Med. Assoc. J.*, 59: 58 (July) 1948.

Transabdominal vagotomy was performed in 66 patients with peptic ulcer. Diarrhea developed in 23; a severe hypoproteinemia was present concomitantly in 2 of this group. On the basis of 39 cases with duodenal ulcer, the author believes that gastric resection is the surgical treatment of choice for duodenal ulcer. Vagotomy should be reserved for these cases in which resection is inadvisable, technically too difficult, or should be employed as an adjunct to resection.

Dramatically successful results were obtained in 10 of 11 patients with marginal ulcers. One case died of intestinal obstruction attributed to gross distension from post-operative intestinal atony. Excellent results from vagotomy were also obtained in 13 patients with high gastric or gastro-esophageal ulcers. Vagotomy is regarded as of greatest value in the treatment of marginal ulceration and high perforating gastric ulcers.

JOSEPH B. KIRSNER

ORR, I. M., AND JOHNSON, H. D. Vagal resection in the treatment of duodenal ulcer. *Lancet*, 253: 84 (July) 1947.

Duodenal ulcer is a disease of increasing frequency and is present in 5 per cent of the population according to Avery Jones. Only a small percentage of these cases, perhaps 20 per cent, require surgery. There are 3 principal operations in common use to-day.

Gastro-enterostomy has been discarded except in cases of long standing pyloric stenosis with low acidity. Subtotal gastrectomy has been generally successful; its average mortality rate is about 2-5 per cent. The incidence of anastomotic ulcers varies between 2-9 per cent. Vagotomy has lately been re-introduced. This procedure produces much less shock, and it has given good results. It accomplishes the double objective of reducing the gastric motility and acidity. Division of the vagi at the lower end of the esophagus eliminates the psychic phase of gastric secretion and abolishes the acid response to hypoglycemia.

Vagotomy alone should never be performed for gastric ulcer because of the danger of malignancy. Three main operative techniques have been described: subdiaphragmatic, transthoracic, and perihial resection per abdomen. The subdiaphragmatic approach gives the greatest number of failures, i.e. incomplete vagal resection. The perihial resection per abdomen was devised by the authors as the method of choice. It affords opportunity for a complete resection of the vagi and may be combined with other procedures on the stomach. Fifty vagotomies were performed by the authors. Subdiaphragmatic vagotomy was done on 15 of these cases, in all of which the resections were incomplete. Three cases were subjected to transthoracic vagotomy. The perihial vagal resection per abdomen was performed on 32 patients. Seven of these later required gastro-enterostomies because of delayed motility. In 16 cases of incomplete resection as determined by the insulin test, 11 had good to excellent clinical results. In 34 cases of complete vagotomy, all gave excellent results.

PHILIP LEVITSKY

PAULS, F., WICK, A. N., AND MACKAY, E. M. Inhibition of gastric ulceration in the rat by o-hydroxybenzoic (salicylic) acid. *Science*, 107: 19 (Jan.) 1948.

Previous work has shown that extensive ulceration develops in the rumen of the rat's stomach following ligation of the pylorus, if the animals have been previously fasted for a length of time which depends upon their age. The ulceration may be inhibited and in some

cases entirely prevented by the administration of certain substances. In examining the activity of mono-hydroxybenzoic acids, one of them was found to have a striking anti-ulcer effect. The sodium salts were used and the therapeutic effect was obtained whether the compound was administered intraperitoneally, subcutaneously or intravenously. Administration of the active compound orally, some little time preceding ligation of the pylorus, showed that it is effective when given in this manner. It is of interest that salicylic acid is a very potent anti-ulcer agent. It also reduces the secretion of gastric juice, as does sodium salicylate in humans. Acetylsalicylic acid is almost as active as salicylic acid in the prevention of gastric ulceration. The activity of other derivatives of salicylic acid, various dihydroxybenzoic acids, and related compounds is now under study.

ALBERT CORNELL

PRIESTLEY, J. AND GIBSON, R. H. Gastrojejunal ulcer: Clinical features and late results. *Arch. Surg.*, 56: 625 (May) 1948. The cause of jejunal ulcer is the same as that of duodenal ulcer. The routine use of gastroenterostomy in the treatment of duodenal ulcer is followed by a relatively high incidence of jejunal ulcer. However, similar use of a moderately high gastric resection with complete removal of the pyloric antrum is followed by a low incidence of jejunal ulcer. Diagnosis of this lesion is usually not difficult and prevention is of paramount importance in any consideration of jejunal ulcer. Treatment is primarily surgical with best results obtained by disconnection of the gastrointestinal stoma, excision of the jejunal ulcer and adequate gastric resection of the posterior Polya type. With this type of therapy, results are satisfactory over a period of 5 to 10 years in about 87 per cent of patients who have undergone previous gastroenterostomy. Results are less satisfactory if the original operation was partial gastrectomy. Late results of vagotomy in the treatment of jejunal ulcer remain to be determined. Of 44 cases in which this procedure was performed, the immediate results have been good in 19 of 24 cases in which

vagotomy was performed for jejunal ulcer that developed after partial gastrectomy and in 19 of 20 cases in which jejunal ulcer developed after gastroenterostomy.

ALBERT CORNELL

DE BUSSCHER, G. La vascularisation de l'estomac ulcéreux. [The vascular anatomy in the ulcerated stomach.] *Gastroenterologia*, 72: 154 (1947).

The distribution of gastric blood vessels was studied in a series of 200 cases, including normal stomachs and the stomachs of patients with duodenal and gastric ulcer. Radiopaque materials were injected into the vessels of resected stomachs and X-ray pictures were taken to show the vascular patterns. In the stomachs of patients with duodenal ulcer, the vascular pattern was similar to that found in the normal stomach. In the case of gastric ulcer, the vascular pattern depended on the location of the ulcer and on the degree of involvement of the deeper tissues with consequent obliteration of blood vessels. However, if a main gastric artery had been partially obliterated, the corresponding area of the stomach was supplied by the other artery. A rich blood supply was found in the antral portion of the stomach.

This study failed to support the view that gastric ulcer is due to a deficient blood supply to the involved area in the stomach.

CHARLES A. FLOOD

FRIEDRICH, L. Ein neues gastroskopisches Symptom beim Zwölffingerdarmgeschwür [A new gastroscopic finding in duodenal ulcer]. *Gastroenterologia*, 72: 299 (1947).

In approximately 50 per cent of patients with duodenal ulcer, gastroscopic examination revealed wide tortuous mucosal folds in the posterior wall of the stomach. These folds resemble the surface of the cerebrum and the author therefore refers to his finding as the "gyrus sign". Evidence of inflammation of the stomach, such as mucous exudate, is lacking. It is believed that the change is due to a viscerovisceral reflex associated with duodenal ulcer. Edema or increased tonus of the muscularis mucosa may explain the changes. The gyrus sign confirms the

diagnosis of duodenal ulcer but does not preclude it.

CHARLES A. FLOOD

ELLIS, M. A study of peptic ulcer in Nigeria. *Brit. J. Surg.*, 35: 60 (July) 1948. A series of 124 peptic ulcer cases, operated on by the author at the African Hospital, Lagos, Nigeria, is reported. The majority of patients were between 30 and 40 years of age; there were 112 males and 12 females. The ulcer was duodenal in 123 and gastric in 1 patient. Three of the former caeses presented themselves as acute perforation, but a history of 2 to 20 years duration was found in the majority. Instead of the clinical picture of pain the majority of the patients had the signs and symptoms of pyloric obstruction. In almost all patients, a moderate-to-severe grade of pyloric narrowing was found at surgical exploration. All patients underwent gastroenterostomy. There was one postoperative death and one patient who developed marginal ulcer.

C. WILMER WIRTS, JR.

## PROCTOLOGY

SKIR, I. Sulfasuxidine in the postoperative care of anorectal conditions. *N. Y. State J. Med.*, 48: 1274 (June) 1948.

Sulfasuxidine was used in the postoperative care of 181 patients who had been subjected to various surgical procedures about the anus. The drug softens the stool, and reduces the bacterial content of the intestines. The drug was given, in 70-100 g. doses, over a period of 7 to 10 days. In 6 patients, this therapy was discontinued after the second day because of nausea, abdominal discomfort, and diarrhoea. The wounds were cleaner but healing had not been accelerated. The patients so-treated, generally required less nursing care, and there was no necessity for enemas.

PHILIP LEVITSKY

ARONSSON, H. Anorectal infections and the sequelae, especially fistulae and incontinence. A clinical study of pathogenesis, prognosis, treatment and complications. *Acta Chir. Scand.*, 96: Supp. 135 (1948). The purpose of this investigative work is to

judge the results of treatment of anorectal infections and to study the causes of postoperative complications. After an extensive review of the literature covering the pathogenesis, prognosis, and therapy of these infections, the author analyzes a series of 1,138 cases. In this series, 61 cases were operated upon by the author including 8 for incontinence.

It is concluded that the crypts of Morgagni are the origin of rectal infections and fistulae. From there, the infections spread via the anal ducts to open submucosally, subcutaneously, or transsphincterally. Fistulectomy should not be resorted to in all cases, because this may entail considerable risk of postoperative incontinence. The recurrence rate after operation is remarkably high—i.e. about 27 per cent. The author believes that this is due to incomplete excision of the internal opening of the fistula. He advises complete excision of the fistula as the operation of choice providing it does not entail division of both the superficial and entire deep anorectal sphincter. Operations for the treatment of incontinence are described.

DAVID A. DREILING

## SURGERY

FRETHEIM, B. Postoperative hypoproteinemia after gastrectomies. *Acta Chir. Scand.*, 96: Supp. 130 (1947).

The author reviews the physiological and pharmacological factors influencing the plasma protein concentration under normal conditions. He discusses causes for the hypoproteinemia occurring in surgical cases, and its consequences and treatment following gastrectomies for ulcer and carcinoma.

In uncomplicated gastrectomies for ulcer, a mild hypoproteinemia may develop due to hemorrhage and postoperative ileus. Its consequences are none. In the complicated ulcer cases and in the carcinoma cases, protein inanition, peritonitis, and shock are additional etiological factors. Here the reduction of plasma protein may be sufficient to produce dehydration and edema. As a consequence there is an increased incidence of gastric retention due to stomal edema, and of wound disruption due to delay of wound

healing. Postoperative proteinemia must be prevented by avoiding blood loss during surgery and by actively replenishing the protein stores with blood and other protein-forming materials.

DAVID A. DREILING

LANDELIUS, E. Results of partial and total gastrectomy in cancer of the stomach. *Acta Chir. Scand.*, 96: 441 (Apr.) 1948.

In an analysis of 172 cases, radical gastrectomies were performed on 87; in 13, a Billroth I type was performed; in 60, a Billroth II; and in 13, a total gastrectomy. The primary mortality rate in the resected group was 23 per cent. About 30 per cent were alive at the end of 5 years, and about 19 per cent at the end of 10 years. In the total gastrectomy group, the primary death rate was 54 per cent. The survival rate was 16 per cent at the end of 5 years, and zero at the end of 10 years. A second series of 20 total gastrectomies done recently at a military hospital is mentioned. The primary mortality in this group was only 10 per cent.

The operative techniques and the indications for each are described. Early postoperative rising and thrombosis prophylaxis are practised. Attention must be paid to the blood count and fluid and electrolyte balance. The diet should be high in fats, proteins, and vitamins and low in carbohydrates. Small frequent meals are given. Iron and liver must be administered because of the danger of pernicious anemia.

PHILIP LEVITSKY

one encountered 3.7 per cent recurrences. No recurrences were seen when the resection was more extensive.

PHILIP LEVITSKY

MELCHIOR, E. Zur Chirurgie des Ulcus ventriculi et duodeni und des Carcinoma ventriculi. [Surgical management of gastric and duodenal ulcer and gastric carcinoma]. *Gastroenterologia*, 72: 361 (1947).

Surgical intervention in ulcer disease should be restricted to chronic cases which resist conservative treatment. When the patient with ulcer has recurrences, has symptoms at frequent intervals in spite of medical management, or has persistent symptoms, he is often found to have a callous lesion. In such cases, gastritis is present. Bleeding or obstruction are also common complications with a callous ulcer. The procedure of choice in treatment is subtotal gastrectomy. When acute perforations of an ulcer occurs, simple closure should be done. Some patients remain symptom-free after closure of a perforation. If symptoms recur later, secondary resection is usually indicated.

In cancer of the stomach, early and radical intervention is essential. Surgery should not be limited to favorable cases because some curable lesions will be overlooked. The total results of surgery in cancer of the stomach are comparatively poor but, as long as no other therapy is available, improvement in prognosis depends on earlier and more extensive surgery.

CHARLES A. FLOOD

VISICK, A. H. Measured radical gastrectomy. Review of 505 operations for peptic ulcer. *Lancet*, 254: 505, 551 (Apr.) 1948.

In a series of 505 radical gastrectomies, the mortality rate was 3.7 per cent. Penetrating ulcers and ulcers of more than 5 years' duration gave twice the above mortality rate. In a follow-up of 430 patients operated on 6 months to 12 years previously, 95 per cent showed satisfactory results. Better results were obtained in males than females. The highest incidence of failures fell in the 5th decade of life. No cases of macrocytic anemia were encountered, but about 20 per cent have secondary anemia in spite of a full diet. In a  $\frac{2}{3}$  to  $\frac{3}{4}$  gastrectomy,

BEST, R. R. Evaluation of colectomy and immediate anastomosis of the rectum. *Arch. Surg.*, 56: 681 (May) 1948.

Up to 40 years ago, the objective in extirpation of rectal carcinoma was preservation of the sphincter mechanism and reestablishment of bowel continuity except when the anal canal was primarily involved. At this time, Miles altered the objective of preserving the sphincter mechanism. Based on the lymphatic and anatomic studies of others, he contended that rectal carcinoma extended in 3 zones—upward, laterally and downward. With a wider excision of tissues in these zones, accomplished by the more radical

abdominoperineal excision, including the entire sphincter muscle area, and establishment of a permanent abdominal colostomy, there was a decided increase in the percentage of cures. This so-called Miles operation, in one or two stages, continues to be the most popular procedure. However, there is now a tendency to revert to the original operations for this malady. Sporadic attempts have been made to develop a technic which would be sufficiently radical to extirpate all malignant tissue and would preserve the sphincter mechanism. In evaluating procedures for preservation of sphincter muscle and function, one must examine morbidity, the rates of mortality, 3- and 5-year survivals, the degree of continence and the element of impotence in male patients. For estimating the 3- and 5-year cures, one must patiently wait for the results. It is possible that the figures for the radical abdominoperineal excision without sphincter preservation will not be reached, but if the percentage of cures is within 10 per cent, it may behoove surgeons to present the problem to the individual patient and allow him to choose between the lessened chance of cure with preservation of that mechanism which rightfully belongs to him, and the radical procedure.

ALBERT CORNELL

### **PATHOLOGY**

DURAN-JORDA, F. Histopathology of the semisquamous epithelial layer in the small intestine. *Brit. J. Surg.*, 35: 84 (July) 1948.

The author describes a very thin, friable, semisquamous, epithelial layer present in the small intestine which has a diapedesic cellular content and contains very small capillaries. He has previously described the existence of this epithelial layer in the stomach, colon and appendix. This layer does not stain with mucus stains and leaves a thin layer of ash after micro-incineration. He also describes the aspect of this layer in strangulation of the bowel, ulcerative colitis, multiple lymphomata, and Meckel's diverticulum. He reports that there are gaps in this particular layer in the normal mucous membrane of the intestine. One is described at the junction between the gastric

mucosa and that of the duodenum, one also in the mucous membrane of the ileum, and a third exceedingly small one in the apex of a villus. The latter has a diameter approximating that of a single red blood corpuscle. These gaps in the mucous membrane are not considered to have pathological significance. Under normal conditions this thin layer probably gives protection to the mucous membrane against both chemical and mechanical irritants, and when destroyed it probably permits more rapid destruction of the underlying mucous membrane.

C. WILMER WIRTS, JR.

### **PHYSIOLOGY: SECRETION**

HANSON, M. E., GROSSMAN, M. I., AND IVY, A. C. Doses of histamine producing minimal and maximal gastric secretory responses in dog and man. *Am. J. Physiol.*, 153: 242 (May) 1948.

Minimal doses of histamine to produce gastric secretion were similar in the intact and the vagotomized total pouch dogs whether the histamine was administered by periodic subcutaneous or continuous intravenous injections. Maximal doses also were identical in both types of dogs. Vagotomy does not alter the secretory response to histamine in the dog. After subcutaneous injection no histamine is inactivated during its absorption from the subcutaneous tissues into the blood. The maximal secretion elicited in both types amounted, on the average, to 80 cc. per hour with a total acid concentration of 140 meq. per liter. Humans are more sensitive than dogs; acid responses were obtained with doses of 0.004 micrograms base per kg. per minute, which is about one-tenth of the dose necessary in the dog. The parietal cell seems to be the most sensitive cell to histamine action although at times the cerebral vessels may be equally sensitive.

ARTHUR E. MEYER

GROSSMAN, M. I., ROBERTSON, C. R., AND IVY, A. C. Proof of a hormonal mechanism for gastric secretion—The humoral transmission of the distention stimulus. *Am. J. Physiol.*, 153: 1 (Apr.) 1948.

Distention of the pyloric portion of the stomach stimulates the secretion of hydro-

chloric acid by the fundic glands. This effect still occurs after interruption of all nervous connection between the stimulated portions of the stomach and the secreting parts. Such an interruption can be accomplished by subcutaneous transplantation of either the pyloric portion or the fundic portion. This experience demonstrates a humoral transmission of the distention stimulus, and constitutes further evidence for the existence of a hormone for gastric secretion.

ARTHUR E. MEYER

### PHYSIOLOGY: MOTILITY

SANGSTER, W., GROSSMAN, M. I., AND IVY, A. C. Effect of d-amphetamine on gastric hunger contractions and food intake in the dog. *Am. J. Physiol.*, 153: 259 (May) 1948.

Subcutaneous administration of d-amphetamine sulfate depressed or abolished hunger contractions in the intact dog for a short time. The concomitant depression of food intake persisted when the gastric motility had fully recovered. Small doses caused restriction of food intake without effect on gastric motility. In animals with vagotomized pouches of the entire stomach, d-amphetamine sulfate caused no suppression of the gastric contractions, even at large dosage, while the effect on the appetite persisted.

ARTHUR E. MEYER

POSTLETHWAIT, R. W., HILL, H. V., JR., CHITTUM, J. R., AND GRIMSON, K. S. Effect of vagotomy and of drugs on gastric motility. *Ann. Surg.*, 128: 184 (Aug.) 1948.

The authors have investigated intragastric pressure, gastric motility and emptying time in vagotomized rabbits, dogs and men. Both rabbits and dogs tend to have normal or hypermotile rather than hypomotile stomachs following vagotomy. In spite of this there is delayed emptying of the stomach in the experimental animals. From these observations and the effects of various drugs there is speculation that the delay in emptying results from failure of the ejection cycle—involving the pyloric canal and sphincter—when operating solely under the intrinsic mechanism of the stomach. Under such a

concept the lack of tone or hypomotility may not be the crucial factor in the delayed emptying of the vagotomized human patient.

Doryl or urecholine by subcutaneous injection will produce contractions, as judged by an intragastric balloon and a manometer, in the vagotomized human stomach equal to or greater than those seen preoperatively.

LEMUEL C. MCGEE

### PHARMACOLOGY

DAVIS, H. A., GASTER, J., MARSH, R. L., AND PRITEL, P. A. The effect of streptomycin in experimental strangulation of the bowel. *Surg. Gyn. Obs.*, 86: 63 (July) 1948.

This study was undertaken to determine the effect of streptomycin in experimental strangulation of the bowel in rabbits. In the control group of 10 rabbits who had not received streptomycin, death occurred within 19 days after operation. Cause of death in 80 per cent of these animals was perforation with peritonitis. In a group of 8 rabbits given 80 mg. streptomycin daily, mortality was 62.5 per cent 19 days following the operation. Early deaths in this group were due to perforation and peritonitis, and later deaths resulted from intestinal obstruction. In a group of 12 rabbits given 200 mg. daily for 7 days and then 100 mg. daily for 21 days more, there was no mortality after a 2-month period.

Because of the action of the streptomycin in preventing perforation and peritonitis, the authors conclude that devascularized bowel (strangulation) gangrene and perforation are due to bacterial invasion of the bowel wall. Successful experimental results led the authors to feel that the administration of streptomycin in adequate dosage might be a valuable adjunct in the treatment of bowel strangulation in humans.

FRANCIS D. MURPHY

### MISCELLANEOUS

THOMPSON, H. Surgical significance of hematemesis and melena. *Arch. Surg.*, 56: 613 (May) 1948.

Whenever severe hemorrhage of undetermined cause occurs, the patient should be under the joint observation of an experi-



enced internist and a competent surgeon. The most frequent cause of hemorrhage from the upper part of the gastrointestinal tract is peptic ulcer. When hemorrhage from this source is sufficiently severe to threaten the patient's life, prompt surgical treatment is indicated for certain groups of patients. In such circumstances, the decision must be made early and the surgeon is in the best position to make such a decision if the patient is under his direct observation. On the other hand, when hematemesis and melena

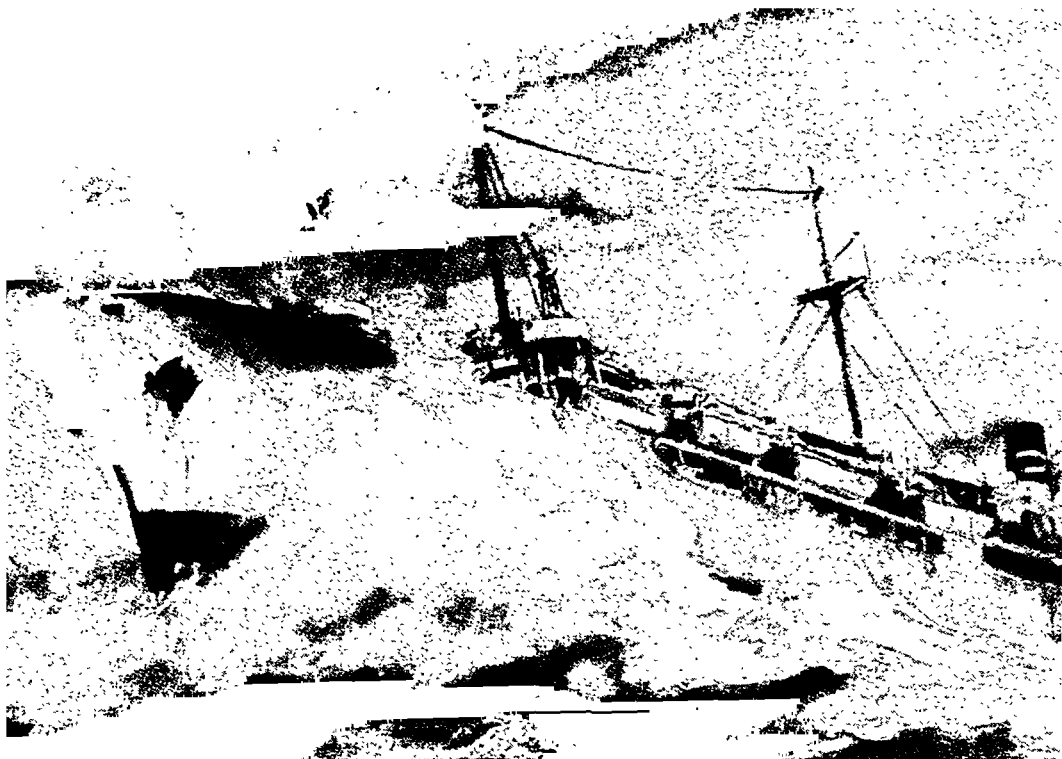
occur in patients in whom peptic ulcer is demonstrable, it must not be assumed that bleeding originates from the ulcer until other causes have been ruled out. In a few cases in which the cause of bleeding after exhaustive investigation remains undetermined, surgical exploration may be warranted as a diagnostic as well as a therapeutic procedure. The pathogenesis, clinical features, indications, contraindications and technic of treatment are discussed.

ALBERT CORNELL

## At the Executive Session

of the American Gastroenterological Association on May 1, 1948 it was moved, seconded and carried that the following by-law be added as Section VI or Article V in the constitution of the American Gastroenterological Association. This by-law is to come up for consideration at the Executive Session of the Association in June 1949. It is as follows:

"There shall also be a limited foreign membership in order to promote better understanding and foster closer relationships between this association and outstanding gastroenterologists of foreign countries outside of the Americas. A small number of individuals from those countries shall be admitted to membership of this association. This classification shall be limited to men and women of exceptional accomplishments in the field of digestion and problems of metabolism and nutrition. They shall be admitted in the regular manner filling out nomination blanks after being duly nominated by two members, not officers, of this association."



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\*Gay, L. N., and Carliner, P. E.: The Prevention and Treatment of Motion Sickness: I. Seasickness, Bull. Johns Hopkins Hospital, in press.

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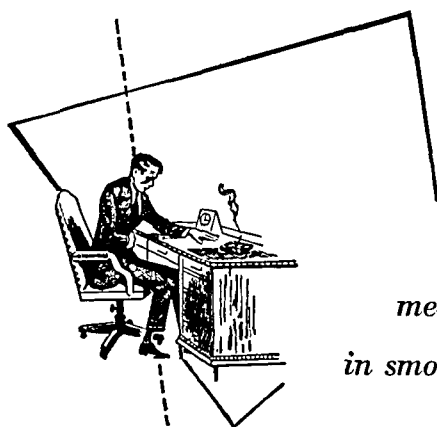
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George B. Jerzy Glass, M.D., and Linn J. Boyd, M.D.

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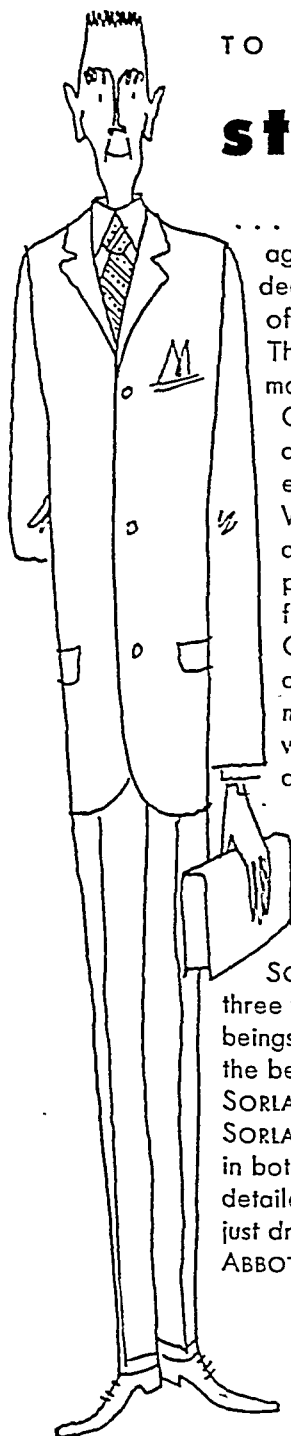
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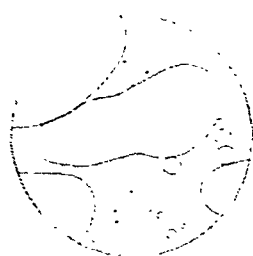
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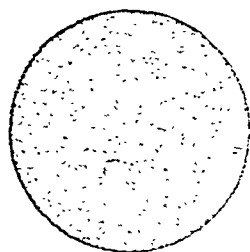
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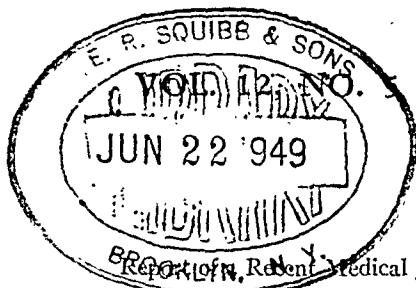
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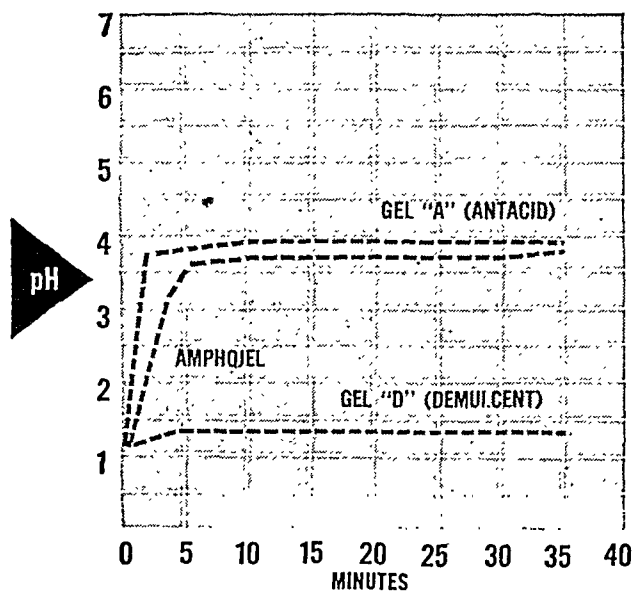
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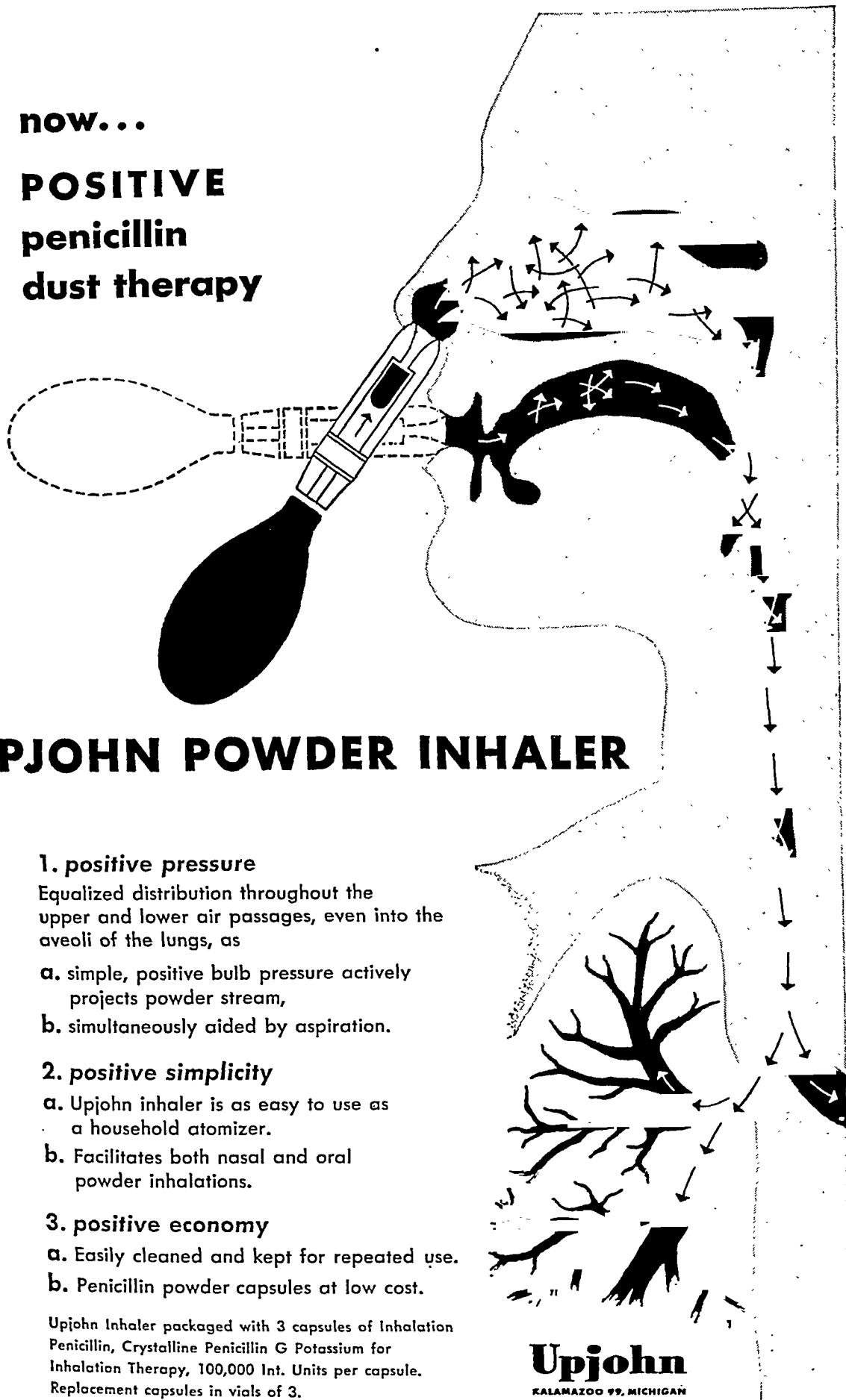
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## VOLUME 12, NUMBER 5

## GASTROENTEROLOGY

*Official Journal of the American Gastroenterological Association*WALTER C. ALVAREZ, *Editor*A. C. IVY, *Assistant Editor*

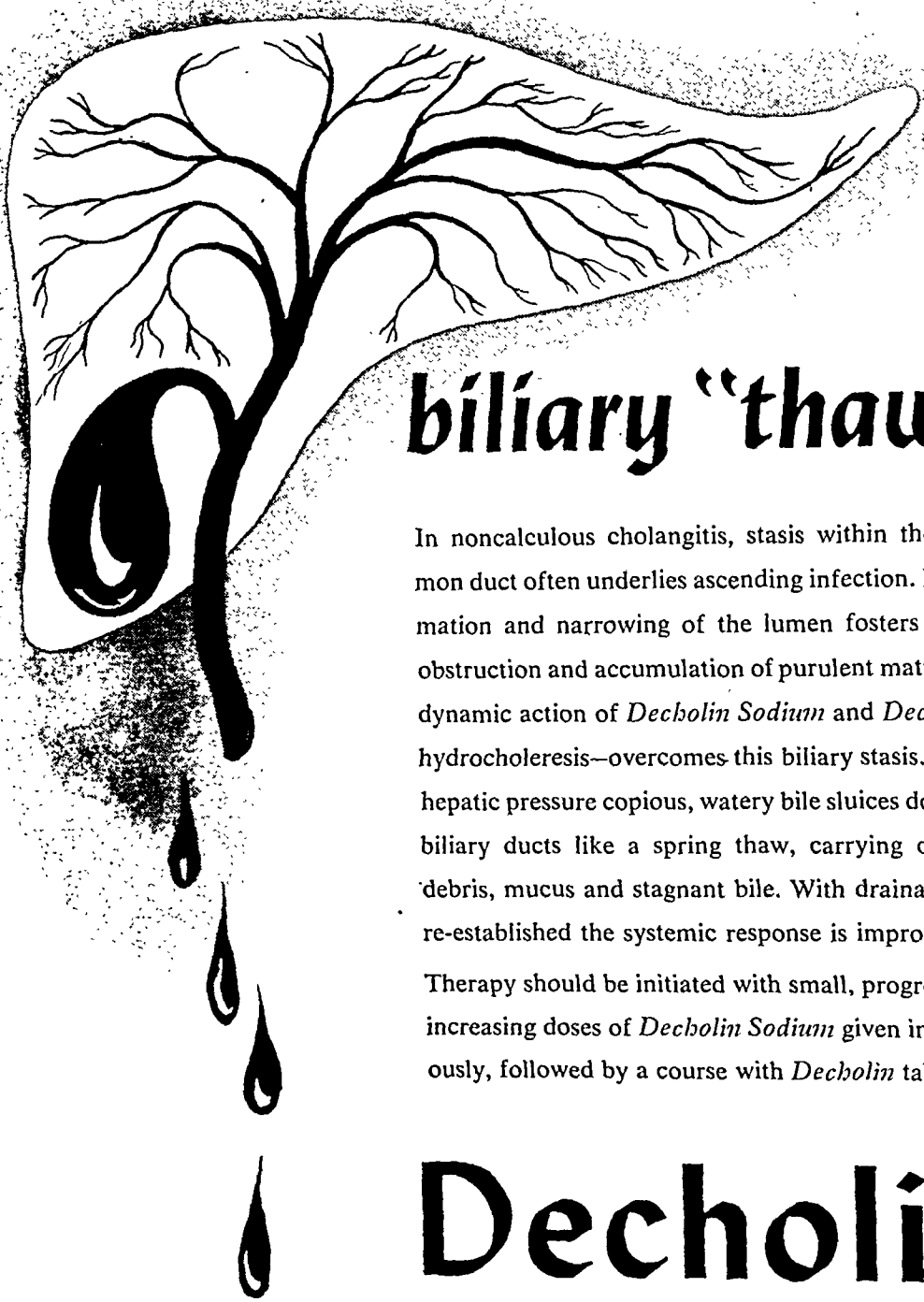
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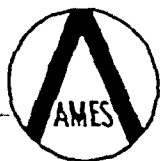
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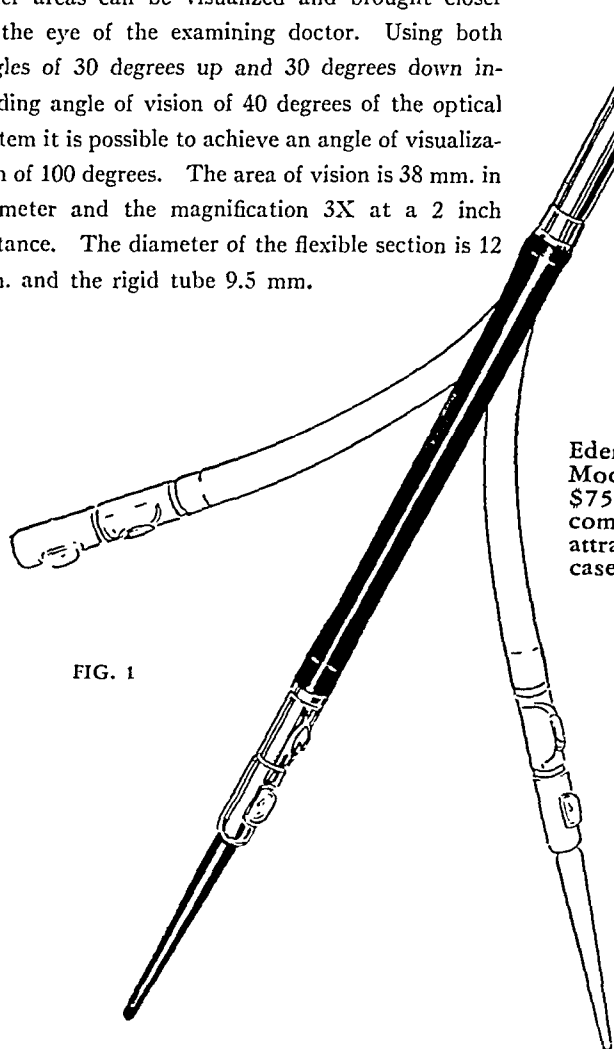


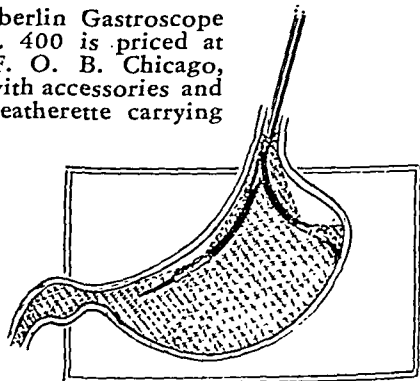
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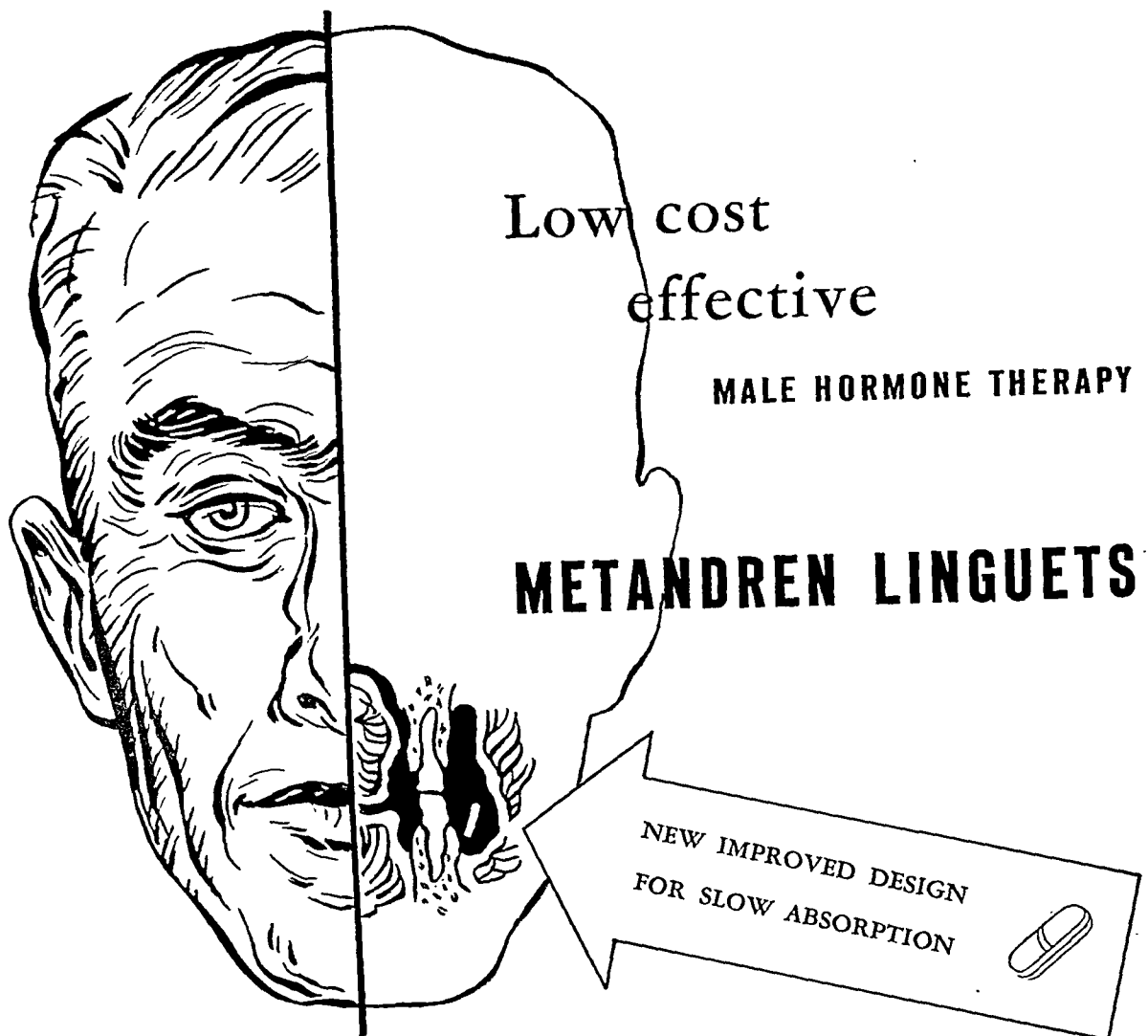
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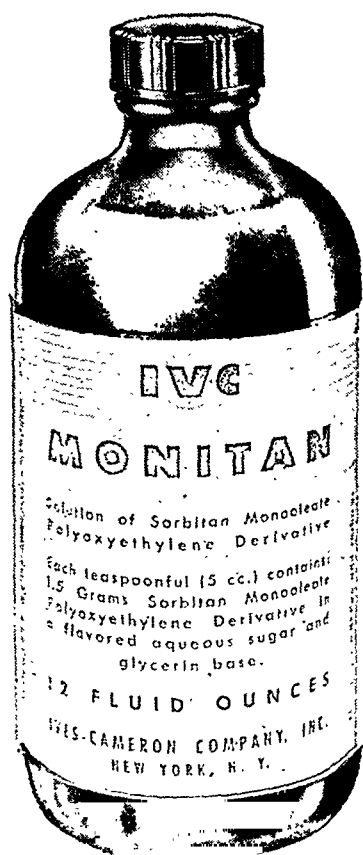
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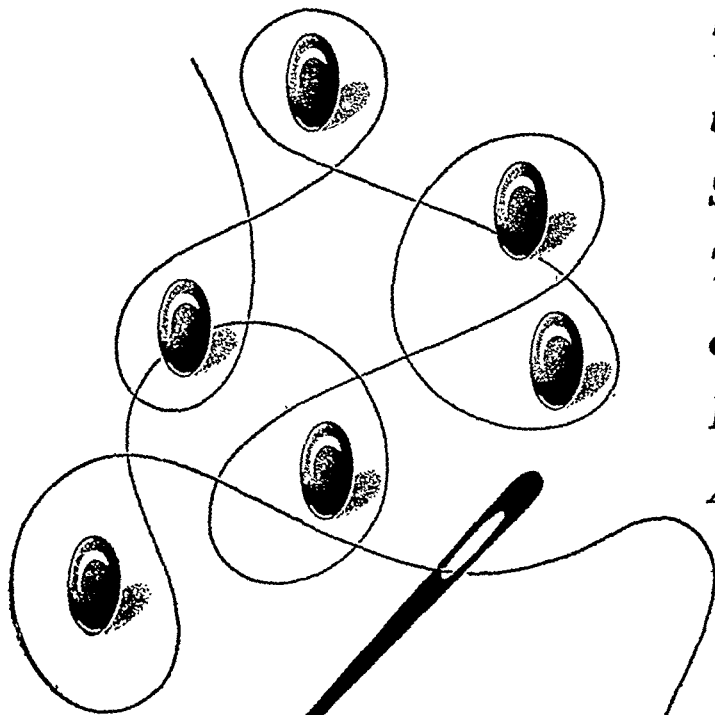
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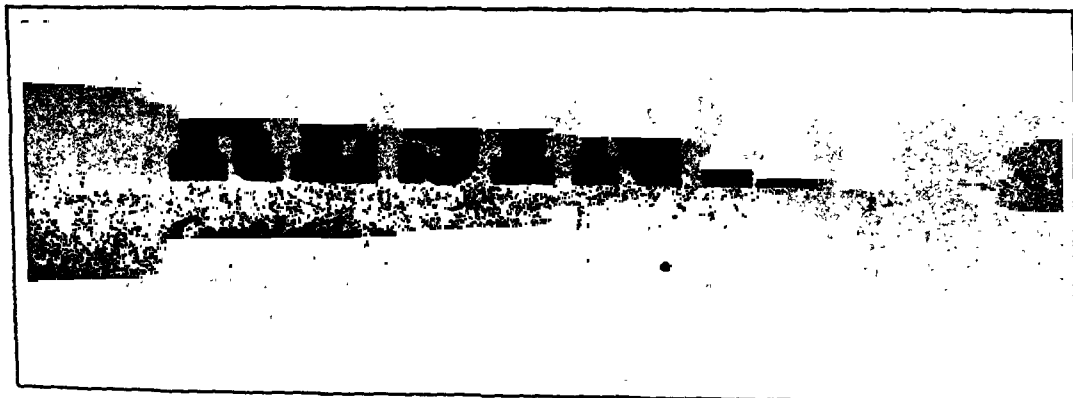
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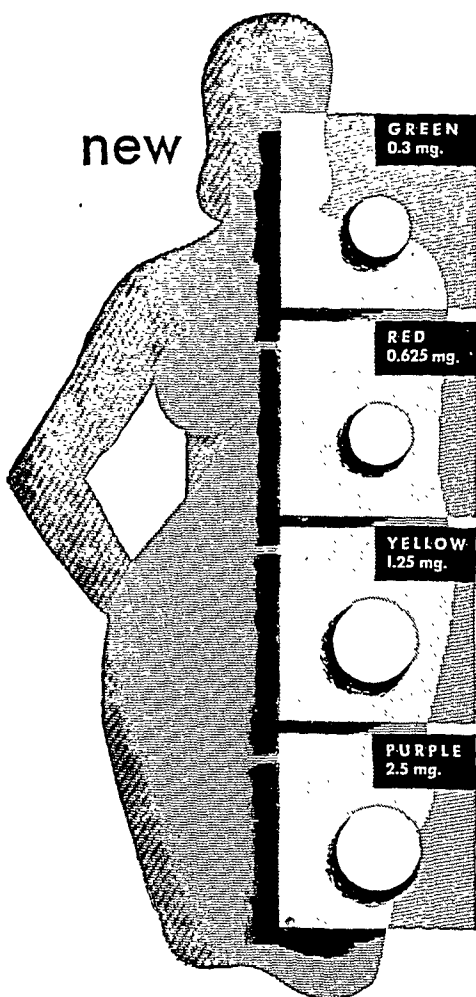
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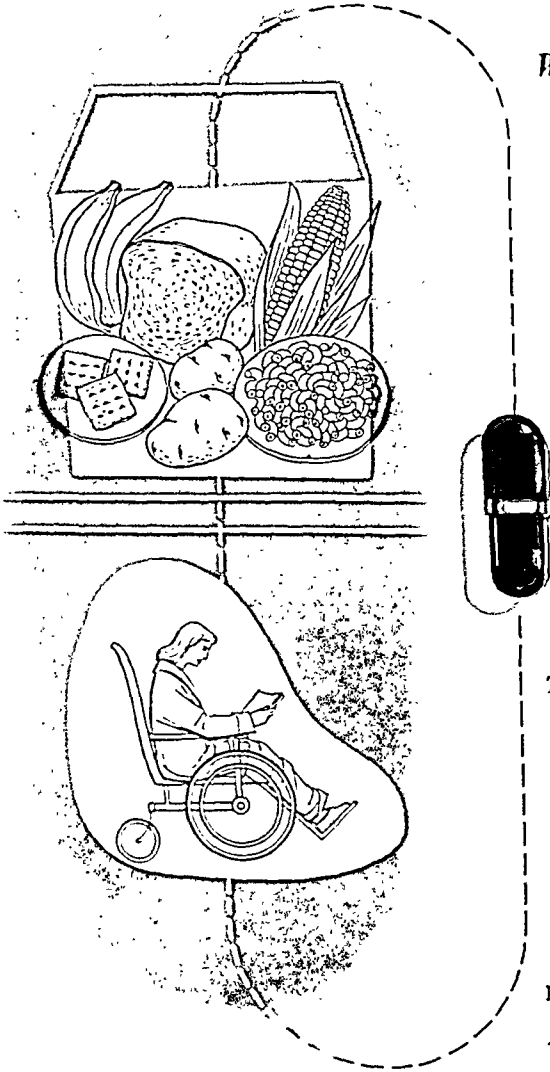
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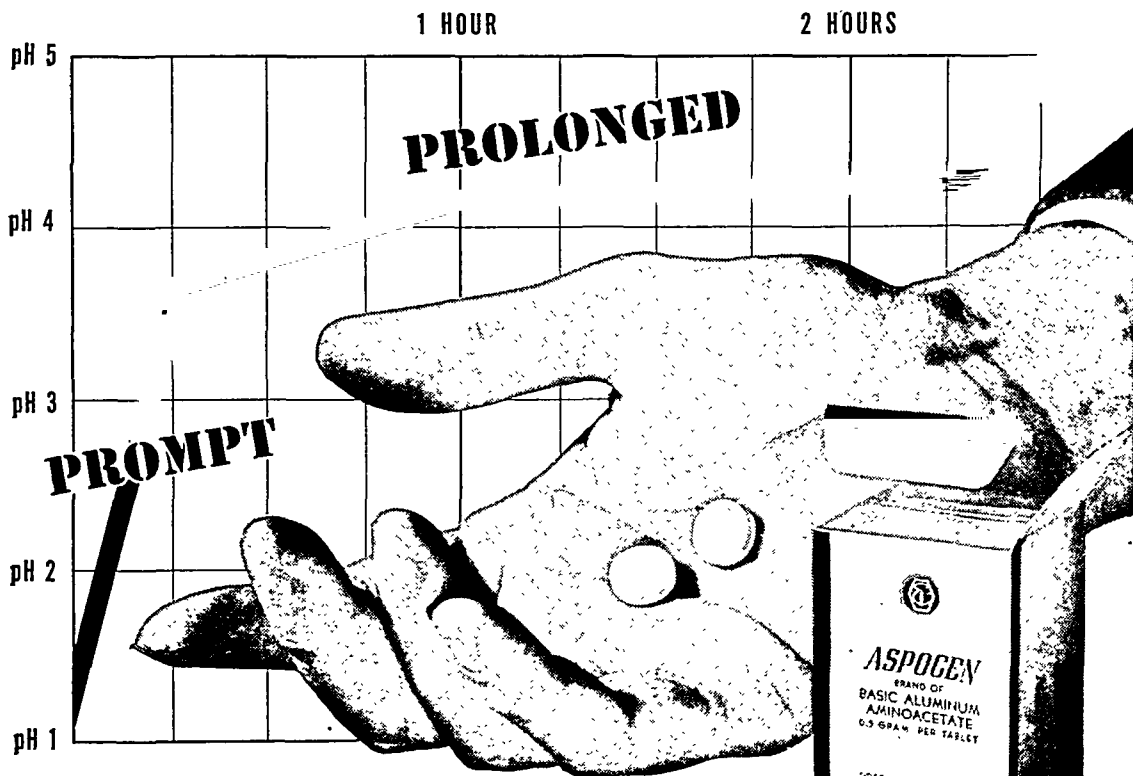
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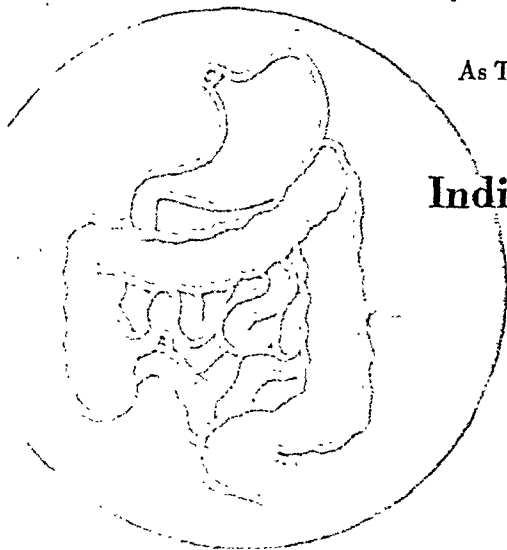
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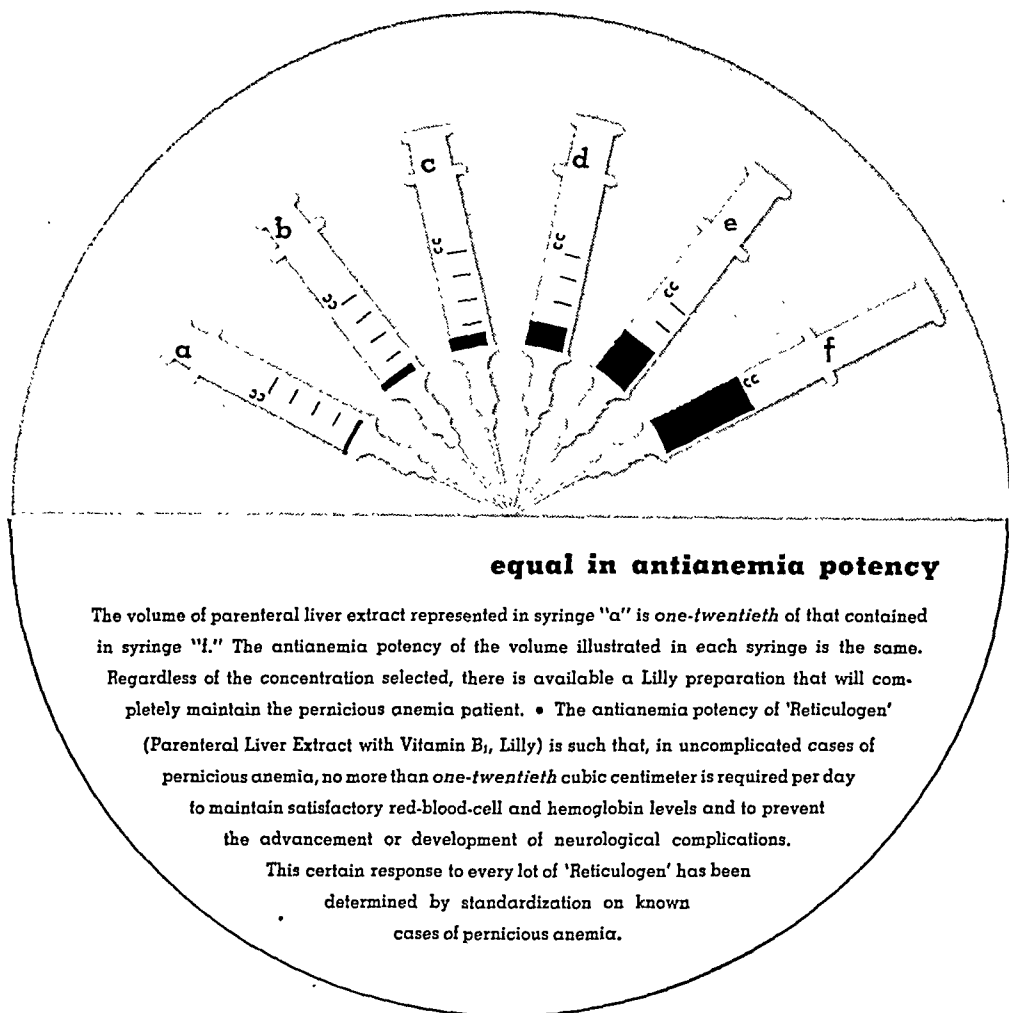
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## REPORT OF A RECENT MEDICAL JOURNEY THROUGH EUROPE

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There was a time, prior to the first World War, when a lengthy visit to European Clinics was considered an essential part of the graduate training of an American physician. The deterioration of the medical centers of central Europe in the years after 1918 made trips of this sort somewhat less popular, and when Hitler came to power the disintegration of German medicine became distressing. Americans still visited European hospitals and clinics, particularly those of the Scandinavian countries and Great Britain, and there found medical work of the highest quality.

The second World War with its terrific impact on European civilization naturally made European medicine even worse. No matter how devoted and able a professor of medicine might be, without adequate funds and facilities, and with too many poorly prepared students in his classes, there was little he could do in the way of research.

Because of the particular interest of the readers of Gastroenterology the following report will be based on observations on gastroenterology and tropical medicine made for the most part in the Scandinavian countries and England.

The Scandinavians, of all people on the continent, are perhaps the most closely allied to us in respect to medical thought. As a group they are quite familiar with American medical thought and practice and many of their medical clinics are closely patterned after our own.

Clinical visits in Copenhagen included one to the celebrated Professor Muelengracht of the Bispebjerg Hospital, whose work on the treatment of bleeding peptic ulcer is well known. He has reversed his attitude on the surgical treatment of severe hemorrhage in older ulcer patients and now advises resection in cases in which the patient continues to bleed on conservative therapy. The indications for surgery under such circumstances are, he thinks, a. profuse hematemesis, b. a previously known ulcer, c. a patient over forty, d. repeated hematemesis and a steady decline in hemoglobin and blood volume in spite of transfusions. He told me of three patients of this type recently operated on all of whom had gastric resections and recovered. He also showed me one patient treated conservatively when seen late after a perforation. There

was gas beneath the diaphragm but the patient appeared to be recovering. Perforations are common at this clinic and simple closure *only* is the rule. It is noteworthy that about 75 per cent of their patients with free perforation have recurrences which bring them back to the hospital within five years.

Vagotomy has been tried briefly in Copenhagen and the verbal reports I heard emphasized some unsatisfactory results. Koester on the surgical service of the Bispebjerg hospital has done transthoracic resection of the cardia and lower esophagus for esophageal varices; I saw one such patient who was doing nicely on about the eighth postoperative day. There is much radical and extensive gastrointestinal surgery done here, including resection of the esophagus for carcinoma, Whipple operations for carcinoma of the pancreas and the like.

Hepatitis, which was widely prevalent in Denmark during the war years, is gradually dropping back down to pre-war levels. Jersilo, who has studied the epidemic features of the disease believes that major epidemics are often followed by a second and later wave of patients with subacute atrophy. This group has a high mortality, and shows a higher incidence of middle-aged women. The reasons for this sex and age incidence is not known. The probable parenteral route of the transmission of hepatitis in hospitalized patients is recognized, and steps are being taken to correct it. Incidentally, they know of no treatment which has any effect upon the course and prognosis of either acute or chronic hepatitis, nor of the cirrhosis which may follow it.

In Stockholm the medical school is centered around the Karolinska Institute, the hospital section of which is one of the newest and best in Europe. It is state owned, receives patients from the surrounding country, the city of Stockholm and "insurance classes". Some private patients are also admitted. The professors give about half time to teaching and research and the balance to private practice. Their earnings are satisfactory, but heavily taxed. State medicine here is said to be working fairly well, but one hears that hospital cases receive too much compensation in comparison to those ill at home, a fact which makes for professional invalidism and for a mass of administrative detail.

The hospital itself has superb equipment and is divided into many small wards with two to four beds, all well furnished, bright and comfortable. One of the show places of the hospital is the auditorium with both indirect and ultra-violet lighting, a remarkably fine epidiascope, and a "blackboard" which projects writing onto the screen used for lantern slides. I attended a staff meeting there and was pushed into a discussion of vagotomy; the experience of the surgical staff there was comparable to that of the Danes.

On the medical wards, which I visited with Professors Svartz and Kellner one sees the usual gastroenterologic problems, notably, cases of peptic ulcer and

chronic ulcerative colitis. Hemorrhagic ulcers are largely treated conservatively; I was struck with the number of older patients with active and apparently intractable ulcers. Prof. Svartz showed me a case of ulcerative colitis in which colonic carcinoma had developed. This had been resected but metastasis had already appeared. I saw one interesting case of intestinal tuberculosis with involvement of the ileocecal coil, which had responded remarkably well to streptomycin. Some other unusual cases were seen, one with a lesion resembling mycosis fungoides, and neutropenia, another with a huge destructive lesion of the antrum and facial bones; the diagnoses of melioidosis and anthrax were being considered.

Adjoining the Karolinska Hospital is the newly completed King Gustav Research Institute; the funds which provided the building and equipment were a birthday gift to the King by the Swedish people. The building is dedicated specifically to research work on rheumatic diseases and anterior poliomyelitis. It contains magnificent equipment including facilities for virus studies, animal rooms, and an electron microscope, constant temperature rooms and a great deal of elaborate chemical equipment. Not many investigators are working there at the present, since the building has just been finished. One man whose work was of interest was Dr. Helander who was working on fluorescent microscopy. He has had beautiful preparations which show the connective tissue localization of such drugs as atabrine and para-amino-salicylic acid.

At Prof. Berglund's Clinic at St. Erich's Hospital some studies on the effects of sympathetic ramisection of the Smithwick type on hypertension were just being completed. This was a remarkably good piece of work and had involved a cooperative statistical study of results from a large number of Scandinavian hospitals. The investigators had collected records of 250 hypertensives operated on, and had followed them over a period of 2-8 years, comparing the survival rates with those of a group of 430 controls, of approximately the same age and sex distribution. Of the individuals with group IV hypertension (characterized by retinal hemorrhages and exudates), three times as many operated patients survived as in the control group with the same grade of hypertensive vascular injury; of the group III patients (characterized by marked cardiac enlargement, inverted T waves in leads I and II, retinal hemorrhages, previous cerebral accidents or proteinuria) operated upon, the percentage of survival was  $2\frac{1}{2}$  times greater than in the control series. In the series of group II hypertensives studied, there were too few deaths in either operated or non-operated cases to permit of statistical comparison; they did note however that a woman in this category had a 75 per cent chance of living out her expectancy and man only a 62 per cent chance. The group I cases (accidentally discovered asymptomatic vascular hyperreactors) were not properly

represented in this series, but they quoted American figures (White et al, J. A. M. A. Vol. 123, p. 937, 1943) to prove that the mortality did not run over 8-15 per cent beyond that expected for the age and sex groups studied.

One resident on Prof. Berglund's service was undertaking a survey of night secretion and gastric acidity levels in normals and in patients with peptic ulcer. He was encountering some not unexpected difficulties in getting satisfactory results but had one interesting development to report; a clinically useful method for pepsin determinations (Biochem. Jour. 42-104, 1948). Lagerlof on the same service was studying the problem of the effect of the sphincter of Oddi on pancreatitis; he had demonstrated rises in blood amylase when secretin was given following the injection of morphine, which produces, as is well known, contraction of the sphincter in sensitized subjects viz. those with biliary dyskinesia.

The last hospital I visited in Stockholm was the oldest, the Serafimer-lazarettet where the medical service was once under the direction of Jacobaeus. The present Professor A. Kristenson, has a thoroughly modern clinic in every sense of the word. I was much interested in the free use of arteriography in the study of cerebral lesions, aneurysms, peripheral circulatory disorders and even abdominal tumors. I was shown one recently made film which had been taken following the injection of diodrast into the abdominal aorta. A splenic tumor was clearly outlined and its blood supply demonstrated, as was also that of both kidneys, one of which contained stones. They deny any trouble from leakage or injury to arteries and do not hesitate to use the method in diagnosis.

The Radiologic department in this hospital was excellent; it was the practice of the clinicians on the service to review all new films with the radiologist before beginning rounds. This practice could be profitably employed in our own hospitals especially on the gastrointestinal services.

At Uppsala, Prof. Ask-Upmark conducted ward rounds for me in the medical service and showed me a remarkably interesting group of patients, many of them with gastrointestinal disease. He had one patient with glomerulonephritis in whom a loop of intestine was being used as a diffusing surface for the elimination of urea. Waldenstrom also of Uppsala is studying the fractionation of plasma proteins in hepatic disease. Since he has had the benefit of the Svedberg ultracentrifuge and the advice of Tiselius, his data are probably as good as can be obtained. It was found that in almost all instances, only the albumin and gamma globulin fractions were affected, alpha and beta globulin remaining remarkably constant. A few sera show high values for beta globulin, and there are still others which show changes in the electrophoretic pattern below the gamma range. The significance of these changes is as yet unknown. The author has seen and is studying a new disease of

unknown etiology characterized by purpura, hyperglobulinism and an elevated blood viscosity.

I was greatly impressed with the type and character of clinical and investigative work which I saw in Copenhagen, Stockholm and Uppsala, much of which cannot be discussed here. All of these cities survived the war with minimal interruption of normal activities. Everyone spoke English (it appears to be a prerequisite for admission to medical school) and their approach to clinical problems was very like our own. It would be well for Americans to follow the *Acta Scandinavica* as carefully as we do our own journals, since medicine in these countries is certainly on a par with the best American work.

#### MEDICINE IN THE BRITISH ISLES

The British, as Edward Weeks has recently remarked, have "imposed upon themselves a set of iron rules" which it seems doubtful if any other nation would accept in peace time. Of these restrictions, the diet is the thing a visitor notices most. It is lacking in many things which we take for granted; one rarely sees eggs, milk, bacon or cream; butter is doled out in microscopic quantities and the meat ration is extremely small (a shilling's worth a week per person). Some idea of the scarcity of meat may be gained from the fact that whale steak is being popularized and that whale liver extract is used in the treatment of pernicious anemia. The only vegetables in common use are potatoes, cabbage and Brussel sprouts. Some fruit is served in hotels, chiefly as compote cooked without sugar. For fresh fruits, one searches the streets for a "barrow boy" and purchases grapes, pears and apples at stiff prices. There is plenty of fish; chicken is served frequently and some game (pheasant, duck and partridge) can be purchased in butcher shops. It is usual to see a sign in butcher shops which says, "We regret that we have no offal today." In the main, British hotel meals are dull and uninspired, the servings are small and one is inclined to welcome any sort of intermeal feeding, however small. The nutritionists point out that the diet is deficient in animal protein, iron and calcium, but that the caloric content is adequate. There appears to be little cheating, incidentally, and everyone is in about the same boat so far as the diet is concerned.

In spite of these restrictions, which must weigh very heavily on the lower and middle classes, there is little evidence of nutritional disease of any type. Anemia in women is perhaps commoner there than in this country; it is of the hypochromic type and is probably referable not only to the diet but to menorrhagia and to the mother's sacrifice of some of her rations to her children. In Edinburgh, Innis told me that the Plummer-Vinson syndrome is common, and in his wards I also saw several severe unclassifiable anemias which were

not responding to treatment. One sees almost no alcoholic cirrhosis or peripheral neuritis; both diseases are rare, due to the short hours during which pubs are open, the scarcity of whiskey and the high prices of all alcoholic beverages (excepting the weak and unsatisfactory beer). Beriberi, pellagra and other major deficiency states are as rare there as in this country.

In spite of dietetic restrictions the children of all classes are probably better fed than at any time in British history. They receive a regular milk ration, cod liver oil and fruit juice concentrates, all at low cost and are everywhere a picture of health. The aged who live alone fare badly, an individual ration book furnishing scarcely enough to meet basic requirements. The sick can obtain special rations on a doctor's certificate; for instance an ulcer patient gets a pint of milk a day, plus an extra egg or two per month. It is hardly necessary to say that one sees few obese people in Britain, and it is equally true that the diet seems to meet the nutritional needs of most persons.

How much more can the diet be altered and still remain adequate? An answer to this question has been attempted by McCance of Cambridge and his associates. They took over the feeding of a group of orphans in the Ruhr, all of whom were well under weight and below the stage of development of their British contemporaries. These children were given all the bread and vegetables they wanted, 200 cc. of milk per *week*, and absolutely minimum amounts of vitamins A, C and D. Neither meat nor animal protein, nor fats were provided on this program, nevertheless these children quickly attained the weight and height of British children of the same age and maintained thereafter a normal rate of growth, with no more intercurrent illness than one would normally expect. Repeated careful and extensive physiologic studies on these children showed no abnormalities whatever. In short, it would appear that given sufficient calories, specific protein and other requirements do not necessarily have to be met.

#### BRITISH MEDICAL SCHOOLS

While some schools were not much more disturbed than our own by the war, others fared very badly. As is well known, practically all medical education in London centered around the former voluntary hospitals. These were largely evacuated during the war, and used as casualty clearing centers; the students and the patients went to rural and suburban hospitals (the former as glorified hospital orderlies and nurses) and most of the faculties donned uniforms or went into other Government services. By the end of hostilities, most of the hospitals had sustained serious injury from bombing and fire, and it was to those damaged structures that the schools returned. In spite of this and the general overcrowding of the medical schools, teaching has now returned to its previous high level. The British are excellent clinicians and

instructors; their students learn the fundamentals of anatomy, physiology and pathology well enough to permit the elimination of many of the laboratory frills from bedside teaching. Everywhere one sees exhibits, charts and diagrams, very thoughtfully arranged and calculated to give a student a clear clinical picture of a disease. They do not hesitate to use every trick of the advertising trade to get a point across; Prof. Learmonth of Edinburgh for instance, had prepared what he called "Mickey Mouse Cartoons" to emphasize the principal points in the diagnosis of gastric cancer, appendicitis and other diseases. They catch the eye and will remain in the memory.

It may also be pointed out that the British are educating a large number of physicians from the dominions and the continent. In one class at the School of Tropical Medicine, there were men from nineteen different countries; one met in every hospital Poles, Hindus, Chinese, South and West Africans (many of them colored), Sikhs, Malaysians and refugees from central Europe. There are numerous programs for graduate teaching, some at the level of "refresher courses" and others calculated to prepare men for FRCP and FRCS examinations. Major General Sir Alexander Biggam is supervising graduate teaching at Edinburgh, and in spite of the crowded conditions at that school (there are 240 students in each of the four medical classes) the faculty is carrying on an extensive and excellent series of courses under his direction. Much of the teaching is of necessity purely didactic, but it is very well done indeed. I attended one two hour lecture on diabetes and its complications which was as fine a review of a subject as one could ask. As lecturers and demonstrators, the British could teach us a good deal.

#### THE SOCIALIZATION OF MEDICINE

British medicine has of course been partly socialized since 1912 by means of the panel system, which concerned chiefly the low income groups. The present 100 per cent socialization dates from July, 1948 and is a truly inclusive affair whereby practically all doctors and dentists become servants of the state and every patient a public ward. There are of course many objections to the plan, but in fairness, it must be said that in the present state of British economy, some such scheme could hardly have been avoided. The weaknesses are pretty obvious and may be summarized briefly. 1. The profession and its auxiliary services weren't ready for it and will not be able to handle the problems presented by it in anything short of a decade. 2. It has greatly increased the outsized army of bureau employees in a country which needs all its available manpower for production. 3. It is enormously expensive. 4. It encourages the professional invalid. 5. It is inclined to overload hospitals with incurable and hopeless cases. 6. It will require a tremendous extension of medical services of all sorts; one of the present crying needs is for clinics and



hospitals in outlying and rural areas. 7. It burdens an already overworked profession with mountains of forms and clinical work. 8. It eliminates healthy competition between doctors and institutions.

On the credit side there is not much to be said except a few obvious things. 1. The schools and teaching hospitals, sure of their budgets and encouraged to train more doctors, are not inclined to complain. 2. The general practitioner, who may not be paid for his excursions into surgical and other special fields, is likely to refer his problems to those better equipped to cope with them. 3. Many individuals will receive services that they could not otherwise obtain and will be restored to at least partial usefulness. A good example of the latter can be seen at the Ministry of Pensions Hospitals at Roehampton which is the major British center for the manufacture and fitting of artificial limbs. I spent an afternoon there and saw dozens of patients of all ages, most of them obviously very poor, being trained in the use of their prostheses. Old diabetics who had lost both legs from gangrene and who had remained sitting so long that they had developed flexion deformities of both hips were being trained to walk; children who had lost arms were being trained along lines which may fit them for productive work.

The notoriously bad British teeth have provided the dentists with a boom business; all of them have their appointment books filled for months in advance and their incomes are correspondingly high. Incidentally the dental bill for the first year of the new scheme will be three times as large as the estimated amount required. The fitting of glasses is another boom business; even the wig makers have profited at the public expense.

In spite of the benefits provided for the public by the act there seems to be a good bit of private practice still going on and there are numerous die-hards in Harley Street who have refused to participate in the program. Considerable organized opposition to the program is forming now under the direction of Lord Horder; his support seems to come both from Harley Street and from rural practitioners. He has had some help from the British press, much of which is anti-Labor.

Incidentally, a very fair and temperate appraisal of the medical practice act has been presented by Feasby (Feasby, W. R.: *Modern Med.* 16: 37-40; 98-100 [Dec.] 1948).

My own observations are in close agreement with those he has presented.

#### TROPICAL MEDICINE

The British Isles are in a sense the home of tropical medicine as an individual specialty. The vast tropical areas which once were a part of the Empire, the investments of British capital in tropical areas, and the fact that British ports receive goods and persons from every corner of the earth are about

equally responsible for the maintenance of interest in this field. The Colonial and the Army medical services have at times attracted some of the best minds in British medicine and a majority of those now practicing or teaching this specialty have a background of experience in one or the other of the services.

The original Hospital and School of Tropical Medicine was founded about fifty years ago near the London docks; it received its major support from the Seaman's Union and Government agencies interested in the health of their personnel, many of them stationed in notably unhealthy corners of the earth. It is said that at the time the school was founded there were usually three Governors of Nigeria; one on his way out to take over the post, one acting in a temporary capacity and a third whose body was being shipped home. Sir Patrick Manson was one of the pioneers in the field and his mantle descended to his son-in-law, Sir Philip Manson-Bahr, currently the president of the Royal Society of Tropical Medicine. This organization, while small, is well financed, owns its own home (Manson House) on Portland Street and edits the premier journal devoted to tropical disease. The School of Tropical Medicine, on Kippel Street near the British Museum, was erected by Rockefeller funds. It sustained severe bomb damage in 1941 and is not as yet fully repaired.

The British army maintains its own school of tropical medicine and hygiene at Millbank. There is also a school at Liverpool, and tropical medical services at two hospitals in that city. At present there is general interest in the subject because of proposed commercial developments in Africa in respect to ground-nuts and cattle.

Through acquaintances at the RAMC school, I was introduced to Dr. Hackett and spent almost a full day in the Wellcome Museum, of which he is the curator. It is probably the worlds' best and most complete collection of material on tropical disease. Considerably more detailed and better documented than most medical museums, it provides a most complete exposition of the subject. Photographs of patients with tropical diseases are uncommonly good and there are many invaluable pathologic and biologic specimens.

I spent a day at the School of Tropical Medicine, chiefly to visit Col. Shortt, whose recent work on the exo-erythrocytic cycle of the malarial parasite has attracted so much attention. First demonstrated in experimental *P. cynomolgi* infections in rhesus monkeys, it was later found in human *P. vivax* malaria, (experimentally produced). The work is continuing to include the field of *P. falciparum* malaria, and in fact a great crop of mosquitoes is being raised for the transmission of that disease in what are certainly the warmest rooms in London. For those not familiar with the subject, it may be said that Shortt's work demonstrates where the malarial parasite resides prior to the initial febrile paroxysm and where it probably remains between relapses. Schizonts have been seen in the liver in all stages from their formation to their rupture,

releasing the parasite into the blood stream. (Shortt and Garnham. Trans. Roy. Soc. Trop. Med. & Hygiene, XLI, 785, May 1948)

I made rounds in two London hospitals with tropical medical services. At Roehampton Drs. Napier and Caplan showed me some interesting material, including persistent *Strongyloides stercoralis* infection with creeping eruption (due to the migration of the larvae in subcutaneous tissue); recurring and apparently drugfast amebiasis; some patients with so-called tropical hepato- and splenomegaly (which may be due to malnutrition plus heavy malarial infection) and a young British flier with proven hepatic actinomycosis. This young man had received record doses of sulfa drugs (1350 gm.) and penicillin ( $35 \times 10^6$  units); he was greatly improved but still had a large firm liver.

Dr. Caplan is specially interested in the post-dysenteric diarrheas, which he believes may be due to damage to the myenteric plexuses.

The British attitude toward amebiasis, of which they have had a large experience, is of special interest to us. They examine many more stools than is the custom here (6 to 12) and place less reliance on therapeutic tests. Complement fixation methods have been given up. Everyone commented on the emetine fast cases, believing they are due either to a particular strain of the parasite or to an acquired drug fastness because of inadequate early treatment. I saw one patient that had received over 300 grains of emetine and who still had vegetative amoebae in his stools. New drugs of synthetic origin were being used, but with indifferent success. Emetine bismuth iodide is still a favorite remedy. Caplan has gone back to an old remedy, yatren combined with quinoxyl retention enemas, and followed by diodoquin. He reports almost no recurrences on this program which, it will be noted, employs no emetine. Chloroquin is also favored, because of the fact that it is concentrated in the liver and may be useful in treating sinuses from liver abscesses. Such abscesses incidentally are rarely opened; antibiotics and amebicides are pushed first and then closed drainage used if necessary.

Dr. Murgatroyd, successor to Hamilton Fairley, who is ill at present, gave me a most interesting day at St. Pancras Hospital, in temporary use as a tropical disease center. In one visit he showed me two lepers, one a late case with extensive maculo-anesthetic lesions, a claw hand and a Charcot joint; Kala-azar in a child from Malta, with a tremendous spleen and the clinical syndrome of hypersplenism, which had proved resistant to antimony compounds and stilbamidine; an "oriental sore", healing on conservative treatment; numerous seamen with active malaria, chiefly of the malignant tertian type; and some patients with tropical (residual) liver disease of unknown origin, but possibly due to malnutrition and malaria. I was interested to see liver biopsies done there with a modified Gillman instrument—which penetrates the liver deeply and gets a sizeable bit of tissue.

Maegraeth, head of the School in Liverpool is especially interested in the effects of anoxia in producing centrilobular liver necrosis. His associates are studying the dissociation curves of oxyhemoglobin in malaria and the oxygen consumption of the parasite; various methods of measuring liver blood flow are being used as well as other techniques for biologic research. (Ann. Trop. Med. 42: 75, 1948, Lancet 2: 781, 1947)

#### BRITISH GASTROENTEROLOGY

Gastroenterology in Great Britain is a well established specialty with its own society and many well known authorities working in the field. However, there are many hospitals where these cases are handled on the general medical wards. One of the best established clinics for gastroenterology which I saw is at Central Middlesex Hospital, London, under the direction of Dr. Avery Jones. They see about 100 ulcer patients per year with hematemesis and at least 50 acute perforations, in addition to the usual run-of-the-mill cases.

It appears that the bulk of their ulcer patients are admitted because of a major complication, past or present. I saw three patients in one ward who had had resections in the presence of free bleeding; all three were found to have open arteries, in their respective ulcers, and all were recovering. About 50 per cent of patients who have their perforations are back within 2-5 years with intractable and disabling ulcer symptoms.

As in other British clinics the ratio of duodenal to gastric ulcers is low probably 4 to 1 as against 12 to 1 in this country. Consequently, they do not worry as much about the danger of missing a cancerous gastric ulcer as we do, the added increment of gastric lesions being benign and largely responsive to treatment.

Curiously enough, acute catastrophes secondary to cholelithiasis are not as common there as in our wards. Stricture of the common duct is a very rare disease, a tribute to conservative and careful surgery. Their experience with hepatitis has been similar to ours. Banti's syndrome with hematemesis from esophageal varices is common enough at this hospital; they have recently had splenorenal anastomoses done with satisfactory immediate results.

Under Jones' direction a survey of the incidence of peptic ulcer in local industrial plants is being made by Dall. About 10 per cent of the males are affected, the incidence rising with age. Almost half of the patients had had a major complication at sometime or other in the past. These patients carry on remarkably well, losing on an average only about 16 days per year because of their ulcers. How they manage on the present British diet is difficult to understand. Detailed figures will be published shortly by Dall and Jones and should make a most interesting and valuable report.

Dr. Clifford Wilson at London Hospital arranged two good days for me and

on one occasion showed me an unusual group of gastrointestinal problems in his wards. These included a patient with polyserositis, a woman with ascites due to tuberculous peritonitis successfully treated by streptomycin and a man-made hemochromatosis which had followed a long series of infusions of washed red cells for aplastic anemia.

Mr. Harold Rodgers at Queen's University, Belfast, also had interesting gastrointestinal material to show, as did his medical colleague Professor Thompson. Rodgers has quite a series of successful splenorenal shunts to his credit. I was surprised to find that Dr. James Learmonth is the leading protagonist of this operation in the British Isles; he has attempted 21 cases and successfully completed 13, with two deaths. I watched one such operation which he completed in  $2\frac{1}{2}$  hours. He used a left lateral approach resecting the eleventh rib and uniting the veins by direct suture; he often uses vitallium tubes for the union of the veins. He is impressed with the general improvement in the anemia and hypoproteinemia. This phenomenon has been noted elsewhere and is not readily explained on the basis of the change in portal blood flow.

Dr. Himsworth of the University of London, whose contributions to the study of liver disease are well known and whose recent book on the subject is one of the best, is continuing his studies on nutritional liver injury. In rats he is able consistently to produce (by dietetic means) fatty change leading to fibrosis. These changes he believes are due to two distinct deficiencies, of alphatocopherol and of cystine. The vitamin-E-free diets must be started immediately after weaning the rats if the deficiency syndrome is to develop promptly. This phenomenon of storage effect may exist in humans and if so would explain the relatively high resistance of previously well fed individuals to poor diets.

Himsworth told me that there is little alcoholic cirrhosis in England now, for reasons mentioned in earlier paragraphs. He is satisfied that epidemic hepatitis produces at least two residues 1. the minimum degree of damage as described by Barker and Capps and 2. a progressively destructive disease with nodular cirrhosis. He isn't as yet convinced that "cholangiolitic cirrhosis" is a recognizable entity.

The British Society of Gastroenterology met at Birmingham, November 12-13th and the secretary was kind enough to invite me to attend. It was an excellent meeting, devoted largely to a consideration of diseases involving the small intestine. A. C. Frazer, the first speaker, discussed the physiologic mechanics of fat absorption in the small bowel; McClaren showed some remarkable cine-radiographic studies of the small bowel which brought out clearly the pendulum and propulsive movements.

French reported a series of experimental studies to explain the so-called "deficiency pattern" seen on radiologic examination of the small bowel. As

he showed, this can be produced artificially by giving concentrated glucose solutions, alkalies, organic acids, and hydrolysed fats. Mucus in large quantities mixing with the barium, he considered as probably responsible for the picture we ordinarily see.

There was an excellent symposium on the diagnosis and treatment of regional ileitis. The notion that the disease may be of tuberculous origin dies hard. Magnus said that in a recently studied case, he had grown tubercle bacilli from adjacent lymph nodes.

Paulley of Middlesex Hospital reviewed all the available data on Whipples' disease, with particular reference to its rather variable histopathologic picture. Stanley Davidson of Edinburgh brought out some of the reasons why urobilinogen measurements were subject to error, not the least of which was the varying composition of the Ehrlich's aldehyde reagent used. Perhaps the most important paper of the whole meeting was that of Bentley who brought forth evidence to show the existence of an arteriovenous shunt in the submucous vascular layer of the stomach. The proof was furnished by the injection technique of Alfred Barclay and by changes in the oxygen tension of blood drawn from the superficial gastric veins. The shunt mechanism can apparently be temporarily interrupted by a high splanchnic block.

In the numerous hospitals and clinics visited, I saw only one case of sprue, and that a remarkable one which had followed a previous ulcerative colitis. This case was demonstrated to us at Birmingham. It was, however, possible to discuss the spure problem with many men who had seen sprue in the tropics as well as in temperate climates. There was general agreement on two points, 1. the tropical form of the disease is rapidly relieved, if not cured, by folic acid and/or liver, 2. the non-tropical form may go into remission on such treatment but it is in general extremely refractory, if not entirely incurable.

MacFarlane, Reader in Human Ecology at Cambridge, and Bradley of the Ministry of Health in Whitehall both had some tales to tell about recent epidemics of hepatitis. One had to do with an outbreak of the disease in soldiers following visits to tattooing "artists," the other with an outbreak in a Swedish summer hotel opened during the Christmas holidays for a party of skiers. There had been a case of hepatitis in the hotel during the summer and the virus remaining in the frozen sewer connections had reached the hotel water supply in some manner and infected 50 per cent of the winter visitors. These reports emphasize the remarkable vitality of the virus and the ease with which it is transmitted.

Bradley was able to supply figures on the use of plasma in Britain and on the reported cases of serum hepatitis. They are currently using about 15,000 units of plasma per quarter and are receiving reports of only about 75 cases of hepatitis or less per this unit of time. He does not believe that all cases are recog-

nized and reported, nor do I. The incidence of hepatitis following the use of serum from very large pools is high; while that taken from small pools is very much lower.

It may be proper to conclude this report with a personal note. The trip was a very interesting and stimulating one, and of considerably greater value professionally than any which I have enjoyed before. Travel, except by air, is somewhat difficult in these times; getting food is a problem in Britain, and everywhere one has to put up with many little inconveniences not encountered during the pre-war years. One is well received everywhere and people are unusually kind and hospitable. Interest in American opinion is greater than in earlier years, and one is subjected to a barrage of questions on every conceivable subject, medical and otherwise. Many of the physicians are more familiar with the American medical literature than are most of us, and their interests are by no means confined to their own special fields or to professional subjects. The average British physician's classical education is superior to ours; he is well informed in many fields not related to medicine, and he often has a keen interest in the arts, music and history. Fortunately many of these men seem not to be particularly disturbed about their present problems, and they expect not only to survive but to make progress. Contact with such men was an inspiration.

The light of learning, at least as it concerns the medical field has been dimmed in Europe for ten years, but in many institutions it is regaining its former brilliance. There is much to be learned from a visit across the water and one returns with a great respect for the people and a greater measure of sympathetic understanding of their trying problems.

## RECURRENCE OF PEPTIC ULCER IN MAN AS AFFECTED BY TREATMENT WITH AN ENTEROGASTRONE PREPARATION

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### DEFINITIONS

*Enterogastrone* refers to the specific material which is present in the upper intestinal mucosa and is responsible physiologically for the inhibition of gastric secretion and motility which occurs when an adequate concentration of fat or sugar is present in the lumen of the upper intestine<sup>1</sup>. *Urogastrone* refers to the material (other than pyrogen) which is present in urine and inhibits gastric secretion and motility on intravenous administration<sup>2</sup>. In the process of making concentrates of enterogastrone and urogastrone we have directed our attention toward the concentration and isolation of that fraction of the material which inhibits or abolishes gastric secretion. *Anthelone* refers to the material found in urine which has an "antiulcer effect"<sup>3</sup>. The material in our enterogastrone preparation which has an "antiulcer" effect has not been given a name.

### ESSENTIAL FACTS REGARDING ACTIVE INTESTINAL EXTRACTS

An extract of the upper intestinal mucosa of the pig can be made which on intravenous injection in the dog inhibits or prevents histamine from stimulating the secretion of acid by the stomach without causing any apparent side reactions<sup>4</sup>. This extract does *not* significantly inhibit gastric secretion when given orally, subcutaneously, or intramuscularly in five or ten times the intravenously effective dose.

Since acid is unequivocally an important factor in the genesis of experimental jejunal ulcer in Mann-Williamson dogs, it was thought that this ulcer might be prevented by the *intravenous* injection of our enterogastrone preparation. (Such dogs have a gastrojejunostomy with the pancreatic juice and bile diverted into the last 15 cm. of the ileum.) In our hands 98 per cent of 114 control dogs receiving no injections and a *special diet* containing raw pancreas and liver developed jejunal ulcer within 9 months after the operation. On the contrary, only 25 per cent of 25 dogs receiving daily intravenous injections of the enterogastrone preparation developed ulcer. The administration of a control extract made from pork muscle did not prevent the development of ulcer<sup>5</sup>.

It was found that the repeated intravenous injection of the preparation did not markedly affect gastric secretion, except that the usual hypercontinuous secretion did not occur<sup>5</sup>. This caused us to suspect that something other than



the enterogastrone in the extract might be exerting an antiulcer effect. Accordingly the extract was given intramuscularly once daily for one year to eight dogs and only one developed ulcer<sup>6</sup>. This demonstrated that the antiulcer effect of the enterogastrone preparation was not due to the immediate gastric secretory depressant action of enterogastrone.

Having prevented the development of jejunal ulcer for one year in a significant percentage of animals, it was decided to stop treatment to ascertain when an ulcer would develop. In a previous study ulcer was prevented from developing for one year by the administration of aluminum phosphate gel 4 times daily. On stopping the administration of the gel an ulcer appeared within 3 months<sup>7</sup>. With enterogastrone injections, to our surprise, a jejunal ulcer did not occur until 18 months or longer after cessation of treatment<sup>6</sup>. Hence it seemed certain that some resistance to the development of jejunal ulcer had been established by the injection of the enterogastrone-containing preparation.

#### ESSENTIAL FACTS REGARDING ACTIVE URINE EXTRACTS

While the foregoing observations were being made urogastrone was found in the urine of man and dog<sup>2</sup>. Some evidence was provided indicating that there is less urogastrone in the urine of ulcer patients than of normal subjects receiving the same diet<sup>8</sup>. Sandweiss and coworkers<sup>3</sup> found an antiulcer effect (anthelone) in a urine extract which prevented or delayed the development of jejunal ulcer in Mann-Williamson dogs. After cessation of the treatment with the urine extract they also noted the existence of some "immunity" to the development of an ulcer.

*Comment.* Thus, a substance is present in intestinal mucosa (enterogastrone) and urine (urogastrone) which inhibits gastric secretion without causing detectable side reactions and is relatively inactive except when given intravenously. An antiulcer substance is also apparently present in the upper intestinal mucosa and the urine; this substance when given intramuscularly prevents the development of jejunal ulcer in the majority of Mann-Williamson dogs, and confers a variable degree of resistance to the development of ulcer after the cessation of therapy.

Although a gastric secretory depressant and an antiulcer activity can be demonstrated in these extracts, the conclusion that these two activities are due to separate substances is not categorically warranted with the evidence at hand. Before such a conclusion is warranted one of these factors must be isolated in pure form and shown to lack the properties of the other.

#### ASSAY OF THE ACTIVE PRINCIPLES

*Enterogastrone or urogastrone.* The assay of the gastric secretory depressant in upper intestinal mucosa or urine is relatively simple. A standard dose of

histamine is given every 10 minutes to a dog with a gastric pouch. One hour after the output of acid has reached a plateau, the substance to be assayed is injected intravenously, the body temperature being followed. If the substance is potent the output of acid will be significantly decreased without the manifestation of side reactions<sup>4</sup>.

*"Antiulcer substance"*. Unfortunately every method other than the M-W dog which we have tried during the past 4 years for decreasing the time and expense required for an assay has been ineffective. A daily injection for 3 months is required to demonstrate clearly an antiulcer effect in the M-W dog and we treat the animal for at least 9 months before we can feel certain that the development of ulcer has been prevented.

Since it is impractical to assay every batch of intestinal extract made on Mann-Williamson dogs, we have empirically required that 50 milligrams of the final product contain one "enterogastrone secretory unit." This is based on the assumption, suggested by our work on Mann-Williamson dogs, that the enterogastrone and antiulcer effects are proportionately concentrated in the product used. Obviously, this is only an assumption and may turn out to be unfounded.

#### EXPERIMENTAL STUDY IN MAN

Regardless of the facts (a) that we could not directly assay every batch of the enterogastrone containing preparation for "antiulcer substance" and (b) that our produce was effective in preventing ulcer in only 75 per cent of Mann-Williamson dogs, we considered it desirable to determine whether the effectiveness of the "antiulcer substance" could be demonstrated in man.

Our second report<sup>6</sup> provided observations on a total of 58 patients who had a long-standing history of peptic ulcer and who had received intramuscular injections for varying periods of time. In our first report it was pointed out that one or two injections each week had no effect on the rate of recurrences, whereas 3 or 6 injections a week appeared to have a favorable effect.

In our second report it was pointed out that treatment by injections of enterogastrone has no advantage over strict conventional antacid therapy for the management of an exacerbation of peptic ulcer; in fact, when the ulcer was penetrating or the distress very severe we recommended strict antacid therapy as an adjunct for a few weeks. It was concluded that the results with enterogastrone treatment "demonstrated the probability that the material is effective in preventing recurrences during the period of its administration, and for a length of time thereafter of a duration as yet undetermined."

In this paper we are providing our observations on 33 of the 39 clinic patients in our second report and an additional group of 13 clinic patients. The private patients treated by Dr. Atkinson and included in our second report are not

TABLE I  
*Recurrences during and after treatment with an enterogastrone preparation*

PATIENT NUMBER	PATIENT INITIALS	SITE OF ULCER	YEARS PRESENT	MONTHS TREATMENT	MONTHS FOLLOW-UP	DURING TREATMENT				AFTER TREATMENT				REMARKS	
						Frequency		Severity		Frequency		Severity			
						None	Fewer	Same	Less	None	Fewer	Same	Less		Same
Injections 6 times weekly															
1	F. A.	D	11	12	23	x								x	Recurrence at 14 months
2	G. A.	D	27	12	34	x								x	Recurrence at 22 months
3	R. A.	G.D.	6	12	33				x					x	
4	G. B.	D	10	12	15	x									
5	C. C.	J	12	12	20	x								x	
6	F. C.	D	5	7	15	x								x	Operated at 20 months
7	M. C.	D	19	10	25										Organic obstruction; operation at 15 months
8	R. C.	D	15	12	27	x			x					x	
9	W. C.	D	6	9	12				x						
10	E. D.	D	29	9	27	x			x					x	
11	M. F.	D	24	12	12										
12	H. G.	D	17	12	25				x					x	
13	F. H.	D	8	12	32	x									
14	A. J.	D	9	12	14										
15	G. J.	D	11	12	23				x						
16	A. K.	D	31	16	20										
17	B. K.	D	24	12	37	x			x					x	Recurrence at 23 months
18	D. K.	D	13	6	31										Operated at 10 months
19	J. K.	D	6	12	34				x					x	
20	S. K.	D	10	5	52										
21	L. L.	G	6	6	29										
22	E. M.	D	36	9	23	x									Recurrence at 20 months
23	P. M.	D	9	12	31									x	Recurrence at 12 months
24	R. M.	D	7	8	36										
25	R. N.	D	20	12	31									x	

[illegible][illegible]

included in the present report. We have lost track of none of 37 clinic patients injected 6 times a week for 5 to 24 months. We have lost track of 3 of 13 of the clinic patients injected 3 times a week; a fourth died of coronary thrombosis. So, the follow-up on the 46 patients in this report has been very successful.

*The Selection of Patients.* The patients were selected on the basis of the presence of a history of peptic ulcer of at least 4 years duration with frequent recurrences. The average duration of the disease in the 46 patients shown in Table I was 15 years. Ten per cent of the patients had the disease from 4 to 5 years and an additional 33 per cent for from 6 to 10 years, the remaining patients for a longer period.

Each patient was asked for the duration of the longest symptom-free period during the two years preceding enterogastrone therapy. The average was 0.3 years (S.D.  $\pm$  0.3 years). The average longest symptom-free period during their entire history was 1.4 years (S.D.  $\pm$  1.4 years).

Each patient was subjected to an upper gastrointestinal roentgenographic study at the beginning of treatment and this was repeated at monthly or bi-monthly intervals up to 6 months. Another examination was usually made at the termination of the treatment and always if the patients reported symptoms suggesting a recurrence.

*The Experimental Design.* There are two possible ways to design an experiment to test the effectiveness of a therapy. One way is to divide the patients into a treated and a control group, the former receiving the active therapeutic principle and the latter the inactivated principle. The other way is to use the past history of the patient, especially when dealing with a chronic disease, as his own control.

It was decided to use the patient as his own control in this study. This was based on the assumption that a patient who shows periods of distress every week or month, or a pattern of frequent recurrences over a period of 4 years or longer is unlikely to show spontaneously a marked diminution of frequency of recurrences on ambulatory management. The validity of this assumption will be discussed later.

*Therapeutic Regime.* In order to make a valid appraisal of the results, we introduced as few changes as possible in the therapeutic program used previously by each patient, except for the administration of the enterogastrone preparation. When necessary strict management was employed, with frequent feeding of a soft diet and aluminum hydroxide or phosphate gels. In such instances the dietary and antacid program was continued until radiographic evidence of healing was obtained. Only two of the 46 patients were hospitalized.

The enterogastrone concentrate, the preparation of which has been described elsewhere<sup>1</sup>, was given in doses of 200 mg. This amount was dissolved in 4 or 5 cc. of sterile water and injected intramuscularly. Until June 1946 we pre-

pared the material ourselves, and thereafter used a concentrate in the form of lyophilized cake prepared in sterile ampules.\*

Several patients have complained of pain following the injections. One patient discontinued the injections after two weeks because of pain.

## EVALUATION

Each patient was interviewed at length, and a careful history was recorded both at the beginning of therapy and by another examiner at the time of this report. An attempt was made to elicit in objective terms the pattern and

TABLE II  
*Status at six month intervals after beginning treatment*

Months after start of therapy . . . . .	12	13-18	19-24	25-30	31-36	37-42	43-48	49-54	55-60
No. cases . . . . .	46	40	35	29	21	9	6	4	2
<hr/>									
STATUS									
Symptom free	No. . . .	19	20	14	11	8	5	5	4
	% . . . .	41	50	40	38	38			2
Improved*	No. . . .	21	14	14	15	10	3	1	
	% . . . .	46	35	40	52	48			
Not improved†	No. . . .	6	6	7	3	3	1		
	% . . . .	13	15	20	10	14			
Operated upon		3	1	1		1			

\* Definitely fewer recurrences, and in most instances milder.

† Recurrences of same frequency.

character of ulcer recurrences before, during, and after treatment with enterogastrone. In each case the past history as given at the recent interview was compared with the history taken at the time of beginning therapy. The notes on the progress during and after treatment with the enterogastrone preparation were compared with the progress notes made during the periodic routine visits.

Recurrences in each patient were classified as to frequency and severity (Tables I and II). In those instances in which the recurrences are referred to as "less frequent" the differences were pronounced and unquestionable. In some cases we have included as recurrences episodes of distress lasting only one or two days and subsiding spontaneously. In several such instances it was not certain that the patient actually had distress due to an active ulcer.

\* Supplied by the Upjohn Company, Kalamazoo, Michigan,

We have recorded (Table I) an appraisal of the severity of recurrences during and after treatment using objective criteria such as duration of symptoms and time lost from work. This appraisal, of course, is regarded as of limited value because of the important subjective component but it offers some additional clinical information.

## RESULTS

### *The Group Receiving Six Injections Weekly During the Period of Treatment*

Twenty-six of the 37 patients received injections for 12 months or a few months longer. Patients no. 9, 10, 20, 21 and 22 discontinued treatment after 9, 9, 5, 6, and 9 months respectively because they said they felt so well that they could not be persuaded to continue the injections because of the inconvenience. Patients no. 6, 18, 24, and 30 discontinued the treatment at 7, 6, 8, and 5 months respectively because they felt the injections were not helping them. Patient no. 6 had been advised by one of us before he was started on the injections to be operated upon because he had a 24-hour retention; he later submitted to an operation. Patient no. 24 also had a high grade obstruction and surgery had been advised; this patient was helped some by the injections and has not been operated upon though recurrent attacks of distress still occur with dietary indiscretion.

Thirteen, or 35 per cent of the 37 patients were symptom free during the period of therapy after the first to eighth week of injections. In an additional 18, or 49 per cent, the recurrences were fewer and in 14 of the 18 less severe and shorter in duration. Thus, 31 of the 37, or 84 per cent, were improved during the period of injections.

If the two patients with high grade obstruction are omitted, because such cases are not amenable to any type of medical management, then 31 of 35, or 89 per cent were improved and 37 per cent completely relieved of symptoms during the 5 to 12 months' period of injections.

*After Treatment.* Four patients who were symptom-free during the period of injections (no. 8, 13, 20, 27) have had no recurrences for 17, 27, 32, and 52 months. An additional patient (no. 34) who was not definitely benefited during 9 months of injections has been symptom free for 20 months after the injections were stopped.

Seven other patients who were symptom free during the injections (no. 1, 2, 17, 21, 22, 28, 33) developed a recurrence at 12, 14, 16, 20, 22, 22 and 23 months.

Fifteen patients had definitely fewer attacks per year after treatment. In 13 cases the recurrences were milder; in many instances transitory episodes of very mild distress occurred. These were considered recurrences because there

was resemblance to previous ulcer pain, but the patients often stated that it merely "felt as though they were *going* to have an attack". This group includes 3 patients whose treatment ended after 6, 8, and 8 months.

In 11 cases recurrences were experienced at the usual rate; four of these discontinued injections at 4, 5, 6, and 7 months, and submitted to operation a few months later. The remaining 7 patients completed a year's treatment. In 4 cases the recurrences were milder; in one the same, and in two more severe than previously.

### *The Group Receiving Three Injections Weekly*

*During Treatment.* Six of the 9 patients were free of complaints attributable to ulcer after the eighth week of injections and remained so for the entire year. The remaining 3 patients had fewer episodes of ulcer distress, and in two the distress was less severe than usual. All patients completed 12 months of injections.

*After Treatment.* In 3 of the 6 patients (no. 1, 9, 5) no recurrence of symptoms has occurred at 34, 47, and 54 months. In two additional cases (no. 3 and 4) after a few mild episodes of distress during the period of injections, there have been no subsequent recurrences during 57 months.

One patient (no. 8) had a recurrence at 33 months and was submitted to surgery. Two patients (no. 2, 7) had recurrences at 15 and 35 months and responded to intensive medical management. Another patient (no. 6) was not benefited by the injections.

Four additional patients were lost track of at 6, 24, 31, and 38 months after starting the injections at which time none had experienced recurrences.

### *Both Groups Combined*

The two groups were kept separate to ascertain whether a statistically significant difference might be found in the results. This was done because we had the impression that the enterogastrone preparation used during the period during which most of the injections were given three times a week was more potent than the preparation used during the period when most of the injections were made six times a week. Though the former results appear better than the latter, the difference observed could occur by chance.

Since the difference in the results with six and three injections a week is not significant, the results on the two groups have been combined in Table II. It is believed that the results as shown in Table II represent a more quantitative or accurate picture than those in Table I.

The table reveals (a) that at the end of the first year 41 per cent of the patients were symptom free and an additional 46 per cent had fewer recur-



rences, and (b) that at the end of the second year 40 per cent of the patients were still symptom free and an additional 40 per cent had fewer recurrences.

Recurrences have not occurred in 10 patients for from 10 to 57 months. Recurrences have occurred at from 3 to 23 months after cessation of therapy in 7 patients who were symptom free during the period of 9 to 12 months of injections.

*Symptom Free Intervals.* Another way to evaluate the results, and perhaps more accurate, is to compare the length of symptom free periods before and after therapy.

The average of the longest symptom free periods in the 46 patients during the two years prior to therapy was 0.3 years (S.D.  $\pm$  0.3 years); after the injections it was 0.9 years (S.D.  $\pm$  0.7 years). The difference between 0.3 and 0.9 years could occur by chance less than once in 100 such experiments.

#### DISCUSSION

*Do the results show that the enterogastrone preparation contains an antiulcer substance which tends to prevent recurrences in man?* This is the important question from the viewpoint of research, since if an antiulcer substance effective in man is present in the enterogastrone preparation further attempts to concentrate it should be made.

In evaluating the results from this viewpoint two facts must be kept in mind. One of these facts is that the enterogastrone preparation did not prevent ulcer in all of the Mann-Williamson dogs, and that an ulcer developed in 2 of 7 dogs from 18 to 36 months after cessation of the therapy. This indicates that we should not expect perfect results in the patients and that recurrences were to be anticipated at some time after cessation of the therapy. The second fact is that our patients represented a group prone to have recurrences and difficult to manage by the usual ambulatory methods. Most of the patients were referred to us by their physician because an operation had been recommended.

The most quantitative evidence indicating that the injections had some degree of effectiveness is derived from a comparison of the average longest symptom free period in the patients before and after the administration of the injections. This figure for two years before the injections was 0.3 years and after the start of the injections 0.9 years.

Since there is only a remote possibility that this difference could occur by chance, the injections undoubtedly had a favorable effect on the group as a whole. If we did not have the results on the dogs, one might be inclined to ascribe the favorable results to reassurance derived from a new treatment<sup>7</sup>. Such reassurance is not likely to last for 6 months or longer. Injections have a psychotherapeutic effect as is well known; but injections of distilled water, histidine, emetine, and vaccine had no effect in the prevention of recurrences

according to the studies of Sandweiss<sup>10</sup> and such a psychotherapeutic effect does not continue for months after the cessation of the injections. There is also the possibility that the injections caused the patient to be more "ulcer conscious" and to watch the diet more carefully than previously. On the contrary, the patients as a group were more liberal with their diet than they had been "for years".

It is questionable whether it is proper to compare our results with the enterogastrone preparation with those of others using other methods of management. This is true particularly when relatively small groups of patients are used and when the method of selection of patients may vary as well as the definition of a recurrence or relapse. From the viewpoint of treatment, our experiment is more analogous to that of Sandweiss<sup>10</sup> in which he injected various solutions into peptic ulcer patients. In 94 instances in which parenteral therapy was followed by remission of symptoms there were relapses in 84 to 91 per cent within the following year. In the 16 cases in our group who had been free of symptoms while under treatment and had been followed for another year, 8, or 50 per cent had recurrences. In their patients treated with diet and alkali, with or without hospitalization, 50 per cent were symptom free during the first year. In our series 41 per cent were symptom free during the first year and 40 per cent during the first two years. Raimondi and Collen<sup>11</sup> observed 66 per cent of recurrences in one year in patients on ambulatory management. During two years, only 18 per cent of 113 patients had remained symptom free. Forty per cent of our group of patients remained symptom free for two years. Flood<sup>9</sup>, who placed his patients on an ambulatory management consisting of dietary restrictions and alkalies for a variable period of time after hospitalization observed that 40 per cent of 140 patients remained continuously free of "significant symptoms" for a period of two years, a figure identical with ours.

If the dietary and antacid therapies used in the foregoing reports have any value in preventing recurrences, then, since our figures fall in the same general range, it should be concluded that the enterogastrone preparation has an antiulcer value. Such comparisons, however, are not as meaningful to us as the fact that in our group of patients the average longest symptom free period was increased from 0.3 years before to 0.9 years after treatment.

*Indications for the use of the Enterogastrone preparation in the patient with peptic ulcer.* First, it should be reiterated that we have no evidence showing that the enterogastrone preparation we have used is superior to any other form of medical management of the acute exacerbation of a peptic ulcer. In fact, ordinary strict ulcer management with antacids, antispasmodics and sedatives will give relief from the acute distress more rapidly as a rule. Second, it should be stated that there is no evidence to show that *the present enterogastrone preparation* is superior to ordinary medical management for the majority of

patients with peptic ulcer, particularly in view of the inconvenience, the cost of the product, and the imperfect results. However, our present experience teaches that its trial is indicated in certain patients. These include those patients, who do not have a significant degree of organic pyloric stenosis, who frequently have periods of severe distress while working and attempting to follow adequate dietary and antacid management, and who defer or refuse operative intervention.

Previous observations have indicated that further research should be directed toward isolating the intravenously active gastric secretory depressant in intestinal mucosa (enterogastrone) and urine (urogastrone). The observations reported in this paper, we believe, indicate that further research should be directed toward isolating the antiulcer substance in intestinal mucosa and urine.

Sandweiss and his coworkers<sup>12</sup> have recently reported upon their experience with the treatment of peptic ulcer with enterogastrone. Their results are not directly comparable with ours because they administered the injections for only 3 months. They found that enterogastrone was about as effective as a diet-alkali regime and more effective than injections of histidine or distilled water in controlling symptoms during the first 6 months. However, in their hands enterogastrone treatment for 3 months gave no evidence of reducing the number of recurrences which had occurred by the end of one year from the onset of treatment.

#### SUMMARY

1. Forty-six patients who received a course of enterogastrone injections (in most instances 3 or 6 times per week for one year) and whose subsequent course after stopping the treatment has been followed for as long as 5 years are reported upon.

2. During the year of treatment 41 per cent of the patients were symptom free and an additional 46 per cent had fewer recurrences. At the end of the second year (after discontinuing treatment) 40 per cent had fewer recurrences.

3. The average of the longest symptom free period in these 46 patients was 0.3 year during the 2 year period prior to therapy and 0.9 year after the therapy. The difference between 0.3 and 0.9 year is statistically significant.

4. Our results are sufficiently clear to cause us to conclude that there is probably an antiulcer substance in the enterogastrone preparation which tends to prevent recurrences in man. The purification of this factor is the subject of continuing research.

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## GASTRIC SURGERY: A REVIEW OF THE LITERATURE

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The numerous papers published in 1947 reflect the continued interest and some evidence of progress in gastric surgery during this period. In general, investigation and attempts at clinical evaluation have been directed toward three phases of gastric surgery, namely results of vagotomy, more emphasis on earlier partial resection for benign gastric ulcers and lastly, it was suggested that total gastrectomy might offer better survival rates in the surgical treatment of gastric carcinoma. We believe, however, that the employment of total gastrectomy for all carcinomas of the stomach is based on conjecture and remains to be substantiated by clinical and pathologic study before such a radical surgical procedure is advocated which undoubtedly will increase the postoperative mortality, and may not improve the ultimate results.

Reports of clinical results after vagotomy and of investigation of gastric and visceral physiology in relation to vagotomy continue to dominate the literature. We note a trend to evaluate more critically the results of vagotomy and to draw attention to undesirable side effects following this procedure. From these studies already begin to appear a crystallization of the real value of vagotomy; in other words, vagotomy should be used cautiously and only with a definite indication of its need and a clear understanding of its dangers.

Pathology will be discussed under its appropriate heading except for two papers which specifically belong to no one heading. The first concerns the distribution of the parietal or acid-producing cell in the normal and the diseased stomach. Meissner<sup>1</sup>, in a study of 200 stomachs, found that in all the number of parietal cells diminished as one approached the pylorus, with fewer cells of this type on the lesser than on the greater curvature. There was a quantitative change in these stomachs in that in the carcinomas the number of parietal cells in the body and fundus often were diminished whereas in duodenal ulcer cases this diminution was less frequent. However, in no stomach, even those known to be anacidic, was there complete absence of such cells, for which fact Meissner found no satisfactory explanation. The second paper concerns the so-called semisquamous epithelial layer which may be demonstrated after formalin vapor fixation. Duran-Jorda<sup>2</sup> stated that as long as this layer remains intact, regardless of the condition of the mucous membrane no ulcer can be present. He stated further that there is some evidence to show that carcinoma arises primarily in the mucous membrane with secondary involvement of the semisquamous epithelial layer.

Despite the emphasis placed on earlier diagnoses in carcinoma, no improvements were noted. Papanicolaou and Cooker<sup>3</sup> stated that in the study of 137 patients

among whom 27 had carcinoma, they reported 10 as positive, 7 as suspicious, and 10 as erroneous negatives. One wonders whether clinical and roentgenologic studies would do as well in discovering early carcinoma of the stomach, yet we believe all diagnostic methods should be employed.

Tomenius<sup>4</sup> modified Papanicolaou's method by dripping into the stomach an isotonic solution of soda bicarbonate through a special tube which prevented contamination with other secretions. This solution prevented acid digestion of the cells. His findings in gastritis with acid secretion revealed a preponderance of leukocytes with increased cell density, but in anacidic gastritis, a normal cytologic picture was present. In cases of carcinoma of the body of the stomach leukocytes were marked; in carcinoma of the cardia no leukocytes were present.

According to Benedict<sup>5</sup>, the combined use of the roentgen ray and gastroscope in 19 known cases of carcinoma proved both instruments to be incorrect in but one case. In 10 cases each method confirmed the other's findings. In 8 cases one method alone was correct—6 by gastroscope and 2 by x-rays.

A complication of gastroscopy—pneumoperitoneum without apparent perforation—was reported by Chamberlin<sup>6</sup>. Although this patient had a laparotomy and resection Chamberlin suggested that perhaps in the future needle aspiration and not laparotomy could be done. The wisdom of such a method of procedure is questionable especially with scrotal, carotid sheath, and subsequently developing suprapubic emphysema, as he reported.

#### PEPTIC ULCER

*Physiology and Etiology.* Physiologic investigations have continued, principally on dogs in which ulcers were produced by histamine in beeswax injections, the Heidenhain technic of closed pouches, and the Mann-Williamson operation. This operation apparently produces ulcers in the jejunum in almost 100 per cent of the animals, with perforation occurring in about 72 per cent. However, in a group of 18 dogs so prepared, Salzstein<sup>7</sup> and his group found that 4 did not die and only 11 formed ulcers when they were fed kitchen scraps and given enterogastrone. Price and Lee<sup>8</sup> established pedicle implants of various tissues into the walls of the stomach of dogs which were injected daily with histamine in beeswax. From these experiments they concluded that living organs and tissue of all sorts are susceptible to gastric digestion and that hyperacidity increases the rate of digestion. Stein<sup>9</sup>, working with Grossman and Ivy, attempted to distinguish between the factors of acidity and intraluminal pressure in the development of ulcers and perforation in dogs with Heidenhain pouches. In one group the pouch stoma was closed nine to eighteen days after its formation, and in another group the pouch was aspirated at frequent intervals. Despite pressure variances, all dogs with an average free hydrochloric acid of over 40 milliequivalents per liter had acute ulcers with perforation. Two dogs with low acid values and high intraluminal pressures

did not develop ulcers. LeVeen<sup>10</sup>, washing the jejunum of dogs with acid pepsin solutions of various hydrogen ion values, found that the increasing ulcerative power of the more acid solutions reached a plateau somewhere near pH 1.0. Secretion of mucus increased proportionately with the acidity of the solution whether pepsin was present or not. This mucus protected the mucosa by acting as a mechanical barrier on a surface area decreased by spasm. This spasm can be produced by acid. While acid alone enhanced mucous secretion, it produced no morphologic evidence of cellular damage. The ulcerating effect of the acid was shown to be dependent upon its enhancement of pepsin action rather than upon cellular injury by the acid. Nasio<sup>11</sup> reported that vitamin C aided the healing of, or afforded protection against, ulcers produced by cinchophen in dogs. Friesen and Wangensteen<sup>12</sup> found that if hemoconcentration could be successfully combated in severely burned dogs, peptic ulcerations did not develop.

Wangensteen restated his finding that in dogs resection of 75 per cent of the stomach protected against histamine-provoked ulcer but either a jejunostomy or a resection of 50 per cent of the stomach failed to prevent ulceration. Berg<sup>13</sup> produced what he called gastric ulcers in rats by tying the single antral vessel or one or both vessels supplying the pylorus. These lesions probably should be regarded as infarcts and not as true gastric ulcers.

The fact that normal or low free acid values are found generally in gastric ulcers and that about 80 per cent of patients with duodenal ulcers have hyperchlorhydria, is set forth in several papers other than those by Winkelstein<sup>14</sup>, Jordan<sup>15</sup> and Hollander<sup>16</sup>. Winkelstein<sup>14</sup> stated that this fact is important especially in the consideration of treatment, "No acid—no ulcer." Other etiologic considerations are the psychosomatic and somatopsychic phase as proposed by Jordan<sup>15</sup>. Crohn<sup>17</sup> believed that psychic trauma may lead to recurrences, while Zano<sup>18</sup> analyzed the process as a conflict involving fear and resentment in which the individual feels compelled to function in a certain manner despite anticipation of failure. The large role that emotion plays in gastric physiology has been the subject of reports by Wolf<sup>19</sup>, who observed that resentment and anger caused congestion and redness of the gastric mucous membrane of man. Rodriquez-Olleros<sup>20</sup> reemphasized the importance of dental defects and efficient mastication in gastric disease. Unfortunately, this is too often neglected in the treatment of ulcer and may have considerable significance.

Hollander posed the question, "Are gastric ulcer and duodenal ulcer different diseases?" He thought that they are for there is a difference in the acid and pepsin concentration; there is greater hyperactivity of the motor mechanism in duodenal ulcer; there is a difference in the size of ulceration (gastric 28.5 mm. versus duodenal 5.5 mm., average); there is greater intensity of pain in duodenal ulcer secondary to the hypersecretion and hypertonicity and finally, there is a difference in the sex and age incidence, with duodenal ulcer being most prevalent in the fourth decade (gastric ulcer in the fifth decade). In our series the average age for development of gastric

ulcer was 54 years and the sex ratio for duodenal ulcer was 4 males to 1 female. Ogilvie<sup>21</sup> also believed that gastric and duodenal ulcers are separate diseases.

*Incidence and Statistics.* The annual mortality from complications of peptic ulcer in the United States remains about 10,000. Whereas, in this country, there is little emphasis on difference in the relative incidence of gastric and duodenal ulcer, in Great Britain duodenal ulcer is becoming more common than gastric ulcer, according to Ogilvie. In the Lahey Clinic, duodenal ulcer is much more common than gastric ulcer, 10 to 1. This greater incidence of duodenal ulcer was also remarked upon by Brun and Landelius<sup>22</sup>. An interesting comment on life in the British Isles is the fact that the results in many papers are expressed in terms of patients being able to return to full or partial employment and not in terms of the patient's improvement and comfort as reported in this country. The incidence of peptic ulcer in patients in the older age group was emphasized by Kiefer and McKell<sup>23</sup>. They recorded that 152 patients had their first symptoms when they were more than 55 years of age; 77 of them were past 60 and 24 past 70 years. There were 112 duodenal, 36 gastric and 4 postoperative ulcers, with 55 per cent of them presenting atypical histories. Of the 152 patients, 48 had hemorrhages and 17 repeated episodes with no deaths from primary bleeding but 4 deaths when hemorrhage recurred. Ulceration recurred in 32 per cent; operation was performed on 27 patients (18 gastroenterostomies and 9 resections), with 2 deaths. The operative mortality is high, but in view of the large percentage of previously operated cases these patients constituted a bad risk group.

*Medical Therapy.* Medical reports seem to confirm the value of the use of amino acids in conjunction with the time proven use of bed rest, antispasmodics acid neutralization and frequent feedings. Hardt and Brodt<sup>24</sup> used aluminum hydroxide gel, magnesium trisilicate and mucin. This combination of agents, they concluded from gastroscopic and roentgenologic observations, gave a distinctive coating action which retarded pepsin activity, neutralized acidity without the risk of alkalosis, and delayed the exodus of the therapeutic agents from the stomach. Kimble<sup>25</sup> and Hodges<sup>26</sup>, in separate reports on protein hydrolysate therapy, relieved the symptoms in 37 of 41 patients within an average of four days or less. Kimble gave 6 per cent protein solution by continuous gastric drip intermittently with milk and cream. At times he combined the drip with amino acids by venoclysis. Fourteen of his 15 patients improved. Hodges gave orally a mixture of amino acids and dextromaltose dissolved in water every two hours, with relief of 23 out of 26 patients. Of Hodge's group the ulcers were healed in 12 cases as judged by roentgenologic examination, improved in 8, with evidence of residual spasticity or deformity, and in 3 there were no radiographic changes indicating healing. Ulcer recurred in 5 of these



cases within five months. Balfour<sup>27</sup> warned that even though gastric ulcers appear to heal they may be malignant and that medical management in small chronic gastric ulcers should not be employed as it is rather dangerous. Jordan<sup>15</sup> believes that gastric ulcers should heal completely in three to five weeks, but if they recur, surgical therapy is indicated. Levin, Hamann and Palmer<sup>28</sup> obtained a decrease, enduring for at least five months, in the free acidity of the night secretion of patients with duodenal ulcers by the use of radiation therapy. Bernstein<sup>29</sup> gave 75 patients a series of twenty injections of 0.2 to 0.5 mg. of histamine phosphate for recurrent ulcers; 82 per cent obtained complete relief after less than ten injections. He rationalized that gastric acidity does not interfere with symptomatic relief but that the mechanism of pain in ulcer is basically vascular spasm which histamine relieves by modifying. On the other hand, Dragstedt<sup>30, 31, 32</sup> reported reproduction of the pain of ulcer by instillation of hydrochloric acid into the stomach after vagotomy had produced relief of pain.

*Surgical Indications.* The indications for surgical therapy in cases of persistence of gastric ulcer and for the complications of duodenal ulcer, to paraphrase Sir Heneage Ogilvie<sup>21, 33</sup>, have been altered somewhat in this country. Promulgated especially by Lahey, the idea of surgical extirpation of all gastric ulcers which recur after treatment or fail to heal promptly is gaining momentum. Ransom<sup>34</sup> reported that formerly 18.9 per cent of patients with gastric ulcers were subjected to operation but that now 30 per cent are operated upon. Vagotomy, which abolishes the cephalic phase of digestion, is also changing somewhat the indications for surgical interference in the treatment of duodenal ulcer. The third change has been the earlier use of surgical procedures in bleeding ulcers in patients more than 45 (Lewisohn<sup>35</sup>) and 55 (Moore<sup>36</sup>) years of age. In our experience without question lives can be saved by earlier surgical intervention in selected cases—patients in whom the systolic blood pressure level cannot be maintained above 90 mm. of mercury or whose pulse rates rise to or above 130. There have been no further reports of the nonsurgical method of treating perforation of ulcers.

*Technical Considerations.* Gastric resection<sup>37</sup> appears to be the overwhelming choice in the surgical therapy of gastric ulcer. The type of operation varied with different groups. Ogilvie, of Guy's Hospital, preferred an isoperistaltic anastomosis with the entire proximal loop in the lesser sac, or a Shoemaker modification of a Billroth II with an end-to-end gastroduodenostomy. Ransom believed a retrocolic Hofmeister type of anastomosis is best while Wangenstein<sup>38</sup> performed, when possible, a retrocolic anastomosis with a short afferent loop. In the Lahey Clinic we prefer the Hofmeister type of antecolic anastomosis, with the proximal jejunal loop attached to the greater curvature. The closed lesser curvature is then buttressed against the jejunum which is distal to the anastomosis. Only one paper mentions a jejunojejunostomy as an adjuvant to the resection. Moore<sup>36</sup> believed that in cases in

which obstruction is or has been a feature, a jejunostomy for feeding purposes at the time of the resection is good surgical management; he advocated this procedure if the morning residual is over 300 cc. In our experience we have seen no need for jejunostomy and indeed it only serves to complicate the operative procedure since we have had no cases of obstruction after resection and had no difficulty whatever in instituting early oral feedings. Three approaches have been discussed for high gastric ulcer. (1) Some have advocated vagotomy for this lesion. (2) Colp and Druckerman<sup>39</sup> have carried out a palliative gastrectomy in which a high subtotal resection without excision of the ulcer was performed. In 10 cases there was one death and in the other 9 cases the ulcers have healed. Ransom, however, stated that palliative resection for high ulcers gave unfavorable results. (3) Moore has advocated a transthoracic resection if the ulcer is high. Our belief is that these ulcers should be resected by whatever route proves easiest and is most familiar to the individual surgeon. The majority of ulcers high on the lesser curvature prove to be resectable readily if the lesser curvature is cleaned of gastrohepatic omentum and the esophagocardial junction identified. Certainly vagotomy is an undesirable surgical method for any type of gastric ulcer because of the possibility that the ulcer may be malignant.

The Finsterer exclusion operation and operations which leave behind any of the antrum are universally condemned. Among those definite in their statements concerning the inadvisability of this operation are Ogilvie, Moore, Ransom, Lewishon and Lahey. Ogilvie stated that, in contrast to a 10 per cent rate of recurrence following a good resection, the antral exclusion operation produced a 30 to 40 per cent rate of recurrent ulceration. It is our experience that recurrent ulcer will develop in a high percentage of patients when the antral exclusion operation is used. We have not used this operation for several years and condemn it heartily; furthermore, we have repeatedly seen recurrent ulcers heal with simple removal of retained antrum.

A suggested technic for the innermost layer of sutures in an anastomosis was described by Sneierson<sup>40</sup>. It consists essentially of two sutures starting in the midline posteriorly and ending in the midline anteriorly. He maintained the advantages are that one can easily obtain good closures at the angles, that a locked suture through all layers of the intestinal wall can be continued about almost all of the stoma, and that conversion to the Connell suture is necessary only for a few of the final stitches of each suture. There are several methods by which angle closure can be made just as effectively and the method employed is not significant.

*Subtotal Gastric Resection.* It is a well-known fact that resection for duodenal ulcer carries a slightly higher mortality and is more frequently followed by complications, especially jejunal ulcer, than is resection for gastric ulcer. We have had no recurrent ulcers following adequate resection for gastric ulcer. Partial resections for gastric ulcer produced 92 per cent satisfactory end results according to Ransom. St. John had 85 per cent good end results in 400 cases. In almost all series, mortality subsequent to resections for gastric lesions was less than for duodenal or gastrojejunal lesions. Lahey reported

no deaths in 110 cases of resection for gastric lesions but a mortality of 2.6 per cent in 400 cases of resection for duodenal ulcer and 2.2 per cent in 200 cases of resection for jejunal ulcer. Ransom reported a 7.9 per cent mortality in 188 cases and St. John, 4.6 per cent. Ransom reported poor results in but 5 per cent and jejunal ulcers following resection in 3 per cent; of those developing jejunal ulcers, 75 per cent had Finsterer exclusion operations.

To designate gastric operations more accurately, Lewisohn proposed that a resection, extending below the pylorus, that includes four-fifths of the stomach be termed a subtotal resection; resection of the lower two-thirds of the stomach plus the pylorus and the duodenal ulcer be called partial gastrectomy, and resection in which the duodenal ulcer is not removed (only 5 per cent are such, he claims) be designated palliative resection. This is an excellent terminology. The term, subtotal resection, is often too loosely applied for all types of gastric resection.

Although resections for duodenal and for gastric ulcer are often grouped together, some differentiation should be developed. Moore stated that 2 per cent to 12 per cent of patients develop recurrent jejunal ulcers after subtotal resection for duodenal ulcers. Furthermore, he stated that if a subtotal resection is done for recurrent massive hemorrhage, especially when unaccompanied by pain, the incidence of recurrent bleeding is up to 35 per cent. Mage<sup>41</sup> reported 23 cases of hemorrhage in 456 patients as a late sequel to the Billroth II type of resection for duodenal ulcer. He found that resection produced an achlorhydria in 90 per cent of cases of gastric ulcer in contrast to 50 per cent of cases of duodenal ulcer.

The common indications for operation were intractability, obstruction, hemorrhage and perforation. Percentages of 26.7, 24, 21.3 and 12 respectively for these indications were reported by Bradshaw and Hightower<sup>42</sup>. One wonders if the term intractability should not more often be applied to the patient rather than the ulcer since so often ulcer symptoms persist because of lack of cooperation on the part of the patient.

Mortality for resection disregarding pathologic indications was reported as follows: Brun<sup>22</sup>, 3.5 per cent; Bartels and Dulin<sup>43</sup> a recent rate of 1.6 per cent (8 per cent in 1941 and 28 per cent in the years 1927 to 1940), and Thompson and Prout<sup>44</sup> 13.3 per cent for cases done by the senior staff, 20.8 per cent for those done by the resident staff and 63.6 per cent when done by the junior staff.

The undesirable postoperative effects which occur in from 5 to 25 per cent of persons following subtotal resection were the subject of studies which gave some illuminating results<sup>45</sup>. The previously called "dumping syndrome," consisting essentially of postprandial fullness, nausea, belching, vertigo, palpitation and sweating with immediate or a delayed onset, was investigated by three groups—Aldersberg and Hammerschlag<sup>46</sup>, Zollinger and Hoerr<sup>47</sup>, and

Gilbert and Dunlop<sup>48</sup> of Edinburgh. Aldersberg and Hammerschlag felt that the early symptoms were of mechanical origin in that the partial stomach emptied rapidly, thereby overflowing the jejunum; the late symptoms arising two to four hours after eating were due to chemical factors—hypoglycemia secondary to an exaggerated postprandial hyperglycemia and occasionally secondary to disturbed intestinal absorption. Zollinger and Hoerr, in a study of 25 cases, found 10 had both hyperglycemia and hypoglycemia, 7 only had hyperglycemia, and 4 only hypoglycemia; the other 4 were normal. They do not feel that hyperglycemia and mechanical distention are satisfactory explanation for the immediate symptoms but that hypoglycemia is the usual causative factor in the late symptoms. Gilbert and Dunlop of Edinburgh in a study of 45 cases demonstrated hypoglycemia one and one half hours after eating in 17 patients. They suggested as a mechanism an early abnormal rise in the blood sugar, which they reasoned, caused a high production of endogenous insulin, the direct result of which was the hypoglycemia—below 60 mg. per cent in 9 cases. All found the following methods of management beneficial: small frequent feedings, high in proteins but low in carbohydrates are given and attempts are made to slow gastric emptying by administering olive oil before eating, or ephedrine before meals, or a high fat diet, or by having the patient assume the horizontal position after eating.

The stoma following resection was defined by Kennedy, Reynolds, and Cantor<sup>49, 50</sup> as the narrow jejunal diameter into which the stomach empties. They effectively demonstrated that that portion of the jejunum along the entire length of the anastomosis becomes actually a part of the stomach wall. By a study of 90 cases they believed that this true gastric stoma displayed a sphincteric action by contracting to one half or one third of its normal diameter. They also mentioned the edema which for about seven days postoperatively causes varying amounts of gastric retention in almost all cases. This edema Efskind<sup>51</sup> thought was probably related more to local trauma than to any acute hypoproteinemia.

In the preoperative and postoperative care of gastric resection the use of vitamin C and amino acids was scrutinized. Zerbini<sup>52</sup> of Brazil gave 1 gm. of ascorbic acid daily, and thought that operation increased the body's need for it, that large concentrations of vitamin C are mobilized in the area of injury. He reported 2 cases in which the vitamin C level seemed to have played a role in shock. Moore stated that if amino acids are given when a patient is in a negative caloric balance, then the amino acids will be deaminized, the nitrogen will be excreted as urea, and the carbohydrate residue will be utilized for energy. Thus, parenteral amino acids given to a patient receiving less than 1500 to 2000 calories a day are a wasteful means of placing a patient in positive nitrogen balance and will not, generally speaking, be utilized for synthesis of

body proteins. He advocated the use of plasma, serum albumin or blood rather than the over-hydration of the patient with a colloid-free solution.

Brown, Calvert and Brush<sup>53</sup> reported 3 cases to make a reported total of 25 cases of gastro-ileostomy. Bartels and Dulin<sup>43</sup> stated that the use of a "T" tube in the common duct when there is danger of injury to that structure is unnecessary, but in their series they reported two operative injuries to the common duct. The identification of the common duct is an absolute necessity in all low-lying ulcers and a "T" tube or catheter in an adherent common duct is not only harmless but will definitely permit identification of the ampulla of Vater and prevent such injuries.

Steinberg<sup>54</sup> reported that with a retrocolic terminolateral large stoma and proximal short loop gastrectomy in 339 primary and secondary operations following which the patients were observed from one to twenty-four years, there have been no jejunal ulcerations.

*Hemorrhage.* Hemorrhage in peptic ulcer, especially in older patients, has been treated with increasing frequency by early resection with or without ligation of the pancreatoduodenal artery. Metheny and Green<sup>55</sup> reported 16 operated cases with one fatality; 13 patients had resections; 1 had no ulcer; 1 had an ulcer in a hernial sac near the aorta, and 1 had a simple pancreatoduodenal arterial ligation. They also presented some equivocal clinical tests to measure the amount of blood loss. Gray<sup>56</sup> advised operation in patients over 50 years within twenty-four to forty-eight hours, adding that 70 per cent of those with two or more episodes of bleeding are likely to have further trouble. This recurrence of bleeding is well recognized and in our experience has been as high as 85 per cent. He believed that it is safe to carry out a roentgenologic examination twenty-four to forty-eight hours after a severe hemorrhage if the patient is not in shock. Massive transfusions given slowly do not elevate the blood pressure so he, therefore, gives transfusions to his patients, gives them adequate fluids, vitamins C and K, atropine,  $\frac{1}{160}$  grain four times a day, and small hourly feedings of milk and cream if the patient can tolerate them. Daly<sup>57</sup> used a combination of thrombin with 0.7 M phosphate buffer by mouth to control hemorrhages. He stated that this regimen should control gastric hemorrhages after four or five doses given at intervals unless there is heavy arterial bleeding or bleeding requiring ligation to control it, in which case surgical intervention is indicated. He reported 21 cases, with a good response in 12. Meulengracht<sup>58</sup> reported his experience with the free feeding policy in bleeding ulcer during the past fifteen years. There have been 26 fatalities in 1,031 patients so treated. Hospital mortality was 2.5 per cent but the net mortality, excluding those dying within twenty-four hours or due to extraneous causes, was 1.5 per cent. He thought that there should not be any serious contraindication to operation, although he preferred not to have

his patients operated on during or just after a hemorrhage, and admitted that operation performed during bleeding was, in a few cases, a life-saving procedure. Operation, Meulengracht believed, should be considered when the patient is over 40 and has bleeding which persists or is repeated and threatens life in spite of repeated transfusions. We suggest that the decision regarding surgical intervention be reached early and that the operation be performed at a time when the surgical risk for the patient is not too great. This will undoubtedly produce far better mortality figures than in the past when surgeons have been asked to operate upon an exsanguinated patient whose tissues and vital cerebral centers have been subject to a long period of anoxia and anemia. Perforce in such cases the mortality and morbidity will be high.

*Perforation.* Literature on perforation of ulcer in 1947 did not contain reports of the nonoperative management of this complication of peptic ulcer. The absence of papers on this particular method is significant. Baritell<sup>60</sup>, however, reported 2 deaths in 7 patients who did have an operation. DeBakey's previously published statistics of collected cases with an over-all mortality of 25.2 per cent, with wound complications in 25.4 per cent and with a mortality increasing proportionately with the age and the length of time before operation were almost universally used as comparison figures. Bloom<sup>60</sup>, using dogs, closed the perforation with a plug of oxycel which was moistened with a 1 per cent solution of sodium bicarbonate. This plug was then painted with pooled plasma and a thrombin moistened graft of posterior rectus sheath and peritoneum was applied with the fascial side in approximation to the oxycel plug and serous coat of the stomach. This graft was then held in contact by a clamp for five minutes. Statistics from other papers gave divergent figures—roentgenologic evidence of pneumoperitoneum ranged from 46 per cent to 77 per cent; mortality from 10.01 per cent (Avent<sup>61</sup>), to 1.1 per cent (Baritell<sup>60</sup>), and to no deaths in 17 cases (Treiger<sup>62</sup>); lack of previous ulcer history from 38 per cent (Treiger) to 13 per cent (Johansson). Bell, Owens and McMurtrie<sup>63</sup> reported a dual perforation which is the forty-fourth case presented, although they stated that the Swedish reported 1 in 200 perforations to be dual. This report also included the treatment of a duodenal fistula by intragastric suction and the use of a precision suction pump (Marsh) connected to the fistula by a catheter surrounded by dressing kept wet continuously with aqueous 1 to 1000 merthiolate. Avent also reported a dual ulcer. Bell et al.<sup>63</sup> stated that there are two or more ulcers in 15 per cent of cases. Rivers<sup>64</sup> listed eight alterations in simple ulcer signs and symptoms that distinguish the emergency syndrome of penetration to the pancreas. The most important feature is the severe, somatic type of intractable pain, often with radiation to the back, which causes the patient to sit with his knees drawn up, the epigastrium held tightly with the hands, and the upper part of the

body bent forward. The laboratory finding of increased blood amylase and lipase is often a confirmatory sign.

Trinca<sup>65</sup>, in a review of 568 cases, believed that abdominal drainage should be used only when one cannot locate the site of perforation or there is a localized collection of pus. He gave the old, oft repeated dictum, "When in doubt, do not drain." His figures seem to indicate that with drainage the period of hospitalization is 50 per cent longer, complications are three times more frequent and mortality three times as great. Treiger's plan of postoperative management has reduced the hospital stay of his patients from 19.5 to 10.8 days. The regimen has no unusual features but in the summation of present knowledge is well conceived. Hirschfield, Abbott and Smathers<sup>66</sup> emphasized that the bacterial factor has the greatest influence on morbidity and mortality. They believed that in order to get more accurate culture reports one should collect 3 cc. of material from the area of perforation for the inoculation of the media. Since 65 per cent of the deaths in their series were directly due to infection, they advocated the use of both penicillin (75,000 to 100,000 units every two hours) and streptomycin (0.5 mg. every six hours). Johansson<sup>67</sup> preferred closure after simple excision of the perforated area, for he thought that recurrence is too high with only simple closure. Trinca utilized an omental tag to close the perforation, as did Werbel, Kozoll and Meyers<sup>68</sup>. Baritell claimed that his is the first report of closure by simply tacking over the perforation some live omentum, usually the gastrohepatic. His plan of procedure included sulfadiazine and 0.6 molar sodium lactate administered intravenously, cotton sutures, and gastric suction for forty-eight hours after operation. He excluded local administration of sulfonamide drugs, preoperative gastric intubation, drains and penicillin. In view of his mortality of 1.1 per cent in 88 operated cases (only 4.5 per cent were operated on over eighteen hours after perforation and 14.77 per cent from twelve to eighteen hours after perforation) and 2 deaths in 7 nonoperative cases, his conclusions are recorded. "Surgeons who persist in advocating such proven unsound principles as drainage of the peritoneum or adding accessory procedures as simple closure may be expected to continue to lose every fifth or sixth patient. The reported mortality rates of from 10 per cent to 25 per cent of operated patients with acute perforations are inexcusably high and can only reflect a failure of surgeons everywhere to apply what is known in the treatment of this emergency, and to do so in every case with the expectation that almost no patient with a perforated ulcer should die if he is seen before he becomes moribund." Omentum, both as a living and as a free graft, has been used for a considerable number of years by many surgeons and to the observing, by Nature herself. Baritell's figures are excellent but his analysis of those figures and the conclusions arrived at as to his method of management, seem to be alloyed with a considerable element of rodomontade.

## GASTROJEJUNOCOLIC FISTULA

Gastrojejunocolic fistula was well discussed by Barber and Madden<sup>69</sup>. After a review of the methods employed, they stated a preference for the management proposed by Pfeiffer. This consists of a preliminary colostomy in the ascending colon followed in six to ten weeks by simple closure of the fistula combined with subtotal gastrectomy. Four weeks later the operation is completed by colostomy closure. In 21 cases handled by this plan a mortality of 4.8 per cent was reported. They preferred this method to that of Lahey and Marshall of ileosigmoidostomy followed later by block resection in which there is a reported mortality of 7.1 per cent. Klingenstein<sup>70</sup> confirmed that this complication is most often seen in men who have had a posterior gastroenterostomy for duodenal ulcer. He warned that a narrowing of the jejunum at the area of repair may result in a blowout of the duodenal stump. We have never seen this complication and, with open communication into the colon and stomach, it must take a high degree of obstruction in the jejunum for this to occur.

## VAGOTOMY

Vagotomy was the primary theme of gastric surgical literature for 1947. The value of vagotomy in the treatment of duodenal ulcer and its complications is still under fire and needs to be clarified and studied further. Orr and Johnson<sup>71</sup>, in succinct phrases, wrote of its position as "Vagal resection—a reconnaissance in force in the war against duodenal ulcer; a lasting success is a triumph of physiological strategy, and a failure spells disappointment but not disaster." Some proposed and have used it successfully for gastric ulcer but physiologically, pathologically and teleologically, extirpation appears to be the better operation for gastric ulcer.

Vagotomy in the laboratory produced the following results. Harkins<sup>72, 73</sup> found that it prevented ulcers produced in rats by pyloric ligation and starvation. He also found that it lessened the incidence of jejunal ulcers in Mann-Williamson dogs. Oliver<sup>74</sup> found that vagotomy done before the Mann-Williamson operation failed to protect the dogs against development of ulcer. Vagotomy subsequent to the Mann-Williamson operation had little or no effect on formation of ulcer. He confirmed the statement that vagotomy reduces the amount and total volume of acid secretion. Saltzstein<sup>75</sup> and his coworkers studied the effect of vagotomy on ulcers produced by the Mann-Williamson operation on dogs which they fed on kitchen scraps instead of pancreas and liver, as did Ivy. Those with vagotomy on the average did not survive as long, although a small percentage developed jejunal ulcers and the incidence of jejunitis and gastric dilatation was much higher. Harris<sup>76</sup>, working with Ivy, found that the motor inhibitory factors in urogastrone and enterogastrone



were active only when the vagi were intact. The 1929 experiment of Hartzell in which vagotomy ablated the cephalic gastric phase of digestion in dogs, with an attending decrease in the hydrogen ion concentration of gastric contents and a constant reduction in the quantity of total and free hydrochloric acid, is frequently quoted, as well as the findings two and one half years later in the same dogs by Vanzant. The latter worker found that excessive mucous secretion was one of the most striking results and that the amount of free and total acid had increased five to six months after operation. There were normal acid curves in 4 and in only 1 dog of the 8 did an absence of free acid remain. The late effects on motility were inconstant and finally most had a return to normal. It was concluded that regeneration of the nerves was not an important factor but that the spontaneous restoration of tone was most probably through the intermediation of the autonomous motor and secretory mechanisms.

A summary of the reported effects of vagotomy in man contains the succeeding facts. It reduces gastric secretion. The acid secretion of the fasting stomach is greatly reduced (946 cc. of pH 1.7 juice to 342 cc. of pH 3.5 juice), although peptic activity is little decreased and the values for combined acid remain relatively high, perhaps indicating that acid neutralization is facilitated. Vagotomy decreased the response of the stomach to alcohol when given intragastrically or intravenously but did not abolish the response to caffeine or to histamine which acts either directly on the parietal cells or on the neuroglandular mechanism. The night secretion in duodenal ulcer cases is reduced to about one seventh of its previous volume. Vagotomy probably reduces mucous secretion since histamine causes the production of little mucus and vagal stimulation produces a juice moderately rich in mucus. However, it is known that sympathetic stimulation causes the prepyloric glands to generate a highly alkaline juice which is low in peptic power and composed mostly of mucus. Motor activity is diminished. This delays emptying. The vagus is the inhibitor to the cardia and pylorus but the motor nerve to the body and antrum. Motor changes distal to the pylorus are transient and ill-defined. Preexisting pain is relieved but pain sensation, which probably follows sympathetic pathways, is not lost. Smith, Ruffin and Baylin<sup>77</sup> found that instillation of 300 cc. of 0.5 per cent hydrochloric acid into a stomach with peptic ulcer produced pain which abated as soon as spinal anesthesia reached the level of the sixth thoracic, but a negative response to the acid was obtained after vagotomy although the sensations of distention, traction and thermal changes were intact. Contrary to this finding, Dragstedt<sup>30-32</sup> reported that, following vagotomy, pain could be reproduced by the oral administration of hydrochloric acid. The pain relief has been attributed both to reduction of acidity and to relief of gastrosplasm. This operation does not affect the utilization and ab-

sorption of protein nor does it disturb the sensations of hunger and appetite. Wolf and Andrus<sup>19</sup>, observing the gastric mucous membrane before and after vagotomy through a gastrostomy, noticed no spontaneous motor activity and only a mild hyperemia of the mucosa after a meal. They also observed that resentment and anger, which caused the gastric mucosa to become red and engorged, produced no similar effects after vagotomy. After vagal section there appears to be an autonomous secretory return in six to twelve months and a restoration of tone usually within a year.

Anatomical knowledge of the nerves is the keystone of the arch of successful operation. Small<sup>78</sup> proposed that the term "vagotomy" denotes a unilateral or bilateral division of the vagus nerves above the cardiopulmonary plexus; that "gastric neurectomy" denotes simple division of the gastric nerves, and that for total or partial resection of the gastric nerves, for example, those fibers below the esophageal plexus, the term "gastric neurectomy" be used. Moore<sup>79, 80, 81</sup> used "vagotomy" to mean section of the nerves and "vagus resection" to mean that a segment of both nerves has been removed. Vagotomy appears to be the term most commonly used, however, and all understand what it connotes. Miller and Davis<sup>82</sup>, from a study of 13 cadaver specimens, and Chamberlin and Winship<sup>83</sup>, from 50 such specimens, concluded that the supradiaphragmatic approach is the better. The latter reported that 73 per cent of nerves were oval and 27 per cent flat and that the level of the lower limits of the esophageal plexus in 69 per cent was 1 to 3 cm. above the top level of the diaphragm, 17 per cent 3 to 4 cm., and in only 9 per cent was it 4.0 to 6.5 cm. Furthermore, they found 60 per cent of the nerves formed single trunks, 16 per cent had primary trunks with 2 or more secondary divisions before going through the hiatus, and 24 per cent had complex patterns. Bradley, Smith, Wilson and Walters<sup>84</sup>, in a study of 111 cadavers (100 adults and 11 children), divided the nerve patterns into four groups: Group I—a common right and left gastric trunk between the esophageal hiatus and 6 cm. above the diaphragm, 64 per cent; Group II—a plexus over the esophagus but forming two main trunks at the hiatus, 7 per cent; Group III—distinct trunks with no branches for 6 cm. above the hiatus, 21 per cent, and Group IV—no consistent pattern, 8 per cent. The gastric nerves were composed of fibers from both vagi as well as sympathetic fibers. Below the hiatus they were able to trace the nerves through a rather constant course. The right nerve, which was the larger in 54 cases, went posteriorly and to the left where, after an interval of 3 to 5 cm., it divided into numerous branches, one of which followed the lesser curvature to the incisura and another the left gastric artery. The left nerve, which had a shorter course, soon lost its identity in the serosa and musculature of the stomach, but constantly supplied a branch which went behind the anterior leaf of the gastrohepatic omentum. Thorek<sup>85</sup> called attention to the fact that the left or anterior nerve hugs the esophagus in contrast to the right or posterior nerve which is separated from it by a slight distance.

Walters<sup>86</sup> preferred the transabdominal or perhiatal approach as one English paper described it. This preference is based on the fact that 92 per cent of the nerves were

found to have a fairly regular pattern, thereby permitting as nearly complete division as through the chest. This approach permits a thorough abdominal exploration with visualization of the pathologic change present and the simultaneous performance of a drainage operation if the operator believes it to be necessary. Moore, Miller and Saunders preferred the transthoracic route; Thompson and James, of England, and Wookey, of Canada, utilized an approach through the left chest. Dragstedt, who originally did most of his cases transthoracically, now prefers the transabdominal route. However, in recurrent jejunal ulcer after resection or gastroenterostomy for duodenal ulcer, the transthoracic approach holds almost universal preference.

Summarizing as accurately as possible without duplication, we found a total of 951 cases of vagotomy reported in the literature<sup>87-116</sup> in 1947. Attempts to recapitulate other variables such as approaches, completeness as determined by the Hollander test, simultaneous or secondarily performed drainage operations such as gastroenterostomy or pyloroplasty, postoperative motility dysfunction, dysphagia and satisfactory or unsatisfactory results defy accurate total tabulation. This seems to be a propitious opportunity to propose the early adoption of a plan whereby deductions and comparisons within reason may be made from fairly uniform reports. Despite this heterogeneous mass of statistics, certain facts can be deduced. The mortality is low, 11 deaths being reported. Dragstedt reported a mortality of 0.4 per cent in 250 cases. The percentages of healed ulcers and satisfactory results at this stage appear to be fairly high. They range from the enthusiastic results of Dragstedt who reported 163 of 170 patients free from ulcer distress without medication or dietary restriction to the satisfactory results (87 per cent) of Moore, and finally to the report by Walters who stated that the results are inconstant, variable and in most cases unpredictable. With the same gradient of fervor as to complications, Dragstedt who excises about 2 inches of the nerve and assiduously prevents postoperative gastric distention, described his complications for the most part as being transitory and inconsequential. Of 61 transthoracic operations, 19 patients had transitory gastric retention and 4 required later gastroenterostomies; of 25 of this group with alteration in bowel habit only 7 had a moderately severe diarrhea lasting two to five weeks. Of 64 cases in which transabdominal vagotomy and gastroenterostomy were performed simultaneously, 8 had transient gastric retention and 4 slight diarrhea of short duration. Of 35 cases of vagotomy alone, 19 patients had transitory gastric retention with 2 patients later requiring a gastroenterostomy. It is of interest to note that Dragstedt mentioned that he does not allow gastric dilatation to occur. He has noticed that there appears to be an association between gastric retention and diarrhea. Of his 74 cases of functional disturbances of a transient nature, Moore described diarrhea in 62 per cent: severe diarrhea in 48

per cent, recovery in 8 per cent, and diarrhea as a remaining major problem in 6 per cent. Grimson encountered 4 severe and 20 temporary cases of diarrhea in 57 cases; 21 of his patients had short-lived dysphagia; 28 were disturbed by postcibal distress for three months—in 11 it persisted and in 6 secondary drainage operations were required. Walters, in 33 simple vagotomies, reported 9 instances of disturbed motility and retention; in 15 gastric neurectomies combined with gastroenterostomy there were 4 patients with disturbed motility, one of whom required operation for an atonic bowel and 2 had intermittent diarrhea. He also listed one case in which acidity and the ulcer recurred six weeks after operation despite a previous condition of achlorhydria. In the 83 cases he reported there were 3 instances of recurrence of ulcer or failure of the ulcer to heal. Both Grimson and Walters feel that serious motility disturbances are more frequent when vagotomy is combined with gastroenterostomy. Dragstedt is now combining a drainage operation with the vagal resection in about 33 per cent of his cases (Grimson performed 21 simultaneous and 5 secondary gastroenterostomies in 57 cases; Walters did only 14 out of 40 without an associated drainage operation).

Pertinent warnings were given concerning thoracolumbar sympathectomies in patients with vagotomy, the use of urecholine, the value of the Hollander test, and the fallacy of continuous gastric suction in determination of the secretory volume. Moore proposed the idea that vagotomy in a hypertensive patient may render the hypertension more rapidly progressive. He, for contrast, related 3 cases in which the patients, subsequent to having splanchnic resections for hypertension, had massive and painless bleeding from duodenal ulcers. He, therefore, concluded that one should approach cautiously splanchnicectomy in the presence of an active duodenal ulcer and vagus resection in the presence of hypertension. Dragstedt recorded no adverse effects from stimulation of the vagi during operative manipulation. He described the transabdominal and Moore the transthoracic technics. Weeks reported a case in which subsequent to vagotomy and thoracolumbar sympathectomy, the patient died as a result of a symptomless perforation. Although Dragstedt early in the year reported on the use of urecholine, he later says that he has not used it nor does he advise its use. Grimson found no restoration of motility with "mecholy," only moderate restoration with "doryl," but good restoration of function with "urecholine," either 5 mg. intramuscularly or 10 mg. three times a day orally. Grimson felt the Hollander test adequate for testing the completeness of the nerve section but Walters and others have pointed out that completeness of division by test does not always determine the relief of symptoms. Motility disturbances were equal in those having either a negative (for example, all fibers cut) or a positive test. Schoen and Griswold listed the fallacies of continuous suction and proposed the injection of a known

amount of phenol red in saline solution for fifteen minutes before aspiration as a means of determining more accurately the secretory volume of the stomach. Alvarez, in a more recent report, gave an excellent review of sixty years of vagotomy and some very pertinent conclusions on this subject. This should be read by all interested in the treatment of peptic ulcers.

#### GASTRIC CARCINOMA

A significant trend in 1947 was the use of total gastrectomy for malignant lesions favorable for cure. Mortality of this operation in private clinics where material is more favorable is now about 16 per cent<sup>117</sup>; of those who survive operation 21 per cent can hope for a survival period of thirty-six months or longer. This is no improvement over partial gastrectomy either in operative mortality (6.7 per cent at the Lahey Clinic) or in ultimate survival. The technic, except for minor differences, is becoming more standardized<sup>118</sup>. Despite this progress, there has been no improvement in the earlier detection of gastric carcinoma. Therein lies the great hope for better survival figures. If diagnostic means could be developed to present these cases earlier to the surgeon, then a decrease could be expected in the 30,000 deaths annually in the United States from gastric carcinoma.

Two well-phrased aphorisms made by Ogilvie<sup>119</sup> in relation to gastric carcinoma are here quoted, "When cancer is in question we should accept the negative warning of a penny weighing machine in preference to the positive reassurance of the ten guinea Harley Street expert." "There is more rejoicing in heaven over the one laparotomy that fails to find cancer than over the 99 that find it too late."

Etiologic and diagnostic aspects of gastric cases were not significantly altered. Strong,<sup>120</sup> injecting mice with methylcholanthrene, raised a strain that in each generation spontaneously developed gastric carcinoma or some closely related biologic entity. Males showed a greater susceptibility to gastric lesions. In his discussion, he compared the kicking of a stone in which the results can be computed to the kicking of a dog where anything may happen. Thus he spotlighted the biologic fact that a cell can be insulted by a multiplicity of agents such as bacteria, a virus, a hormone, or a vitamin but how that cell responds or fails to respond is determined by its intrinsic genetic constitution. It is this genetic concept of the nature of intrinsic biologic variability, together with chemical induction, that makes possible the development of benign and malignant tumors in animals. Comfort, Kelsey and Berkson,<sup>121</sup> in a study of 227 cases, found that subnormal gastric secretory activity was characteristic of precancerous (gastric) lesions regardless of the age of the patient. Jordan reported that free hydrochloric acid was present in gastric carcinoma in 40 per cent of her cases. Engel found 55 per cent to have normal acidity. Kaplan and Rigler<sup>122</sup> found that gastric carcinoma was five to twenty times more prevalent in those with

pernicious anemia; gastric polyps were ten to sixteen times as frequently found in patients with pernicious anemia. In patients with primary hyperchromic anemia Wangenstein<sup>123</sup> placed the incidence of gastric carcinoma at 12.3 per cent, or three times the expected autopsy rate. The average duration of the anemia before the development of carcinoma, when it occurred, was 8.7 years. In another article Rigler and Kaplan<sup>124</sup> suggested that liver therapy contains a carcinogen which may account for the higher incidence of malignant disease rather than the achlorhydria, achylia and atrophic gastritis which usually accompany the anemia. State, Moore and Wangenstein<sup>125</sup> examined a group of 464 patients, over 50 of whom had an achlorhydria to histamine stimulation; 79 of this group had macrocytic hyperchromic anemia. Among these patients, 3 undetected gastric carcinomas and 15 polyps were discovered. The relationship of achlorhydria and polyps seemed to them to be significant. Welch,<sup>126</sup> in his pathologic résumé, reported 40 per cent of polyps to be malignant but 75 per cent of these patients survived five years.

Gessler<sup>127</sup> presented a dissertation on the routes of spread of carcinoma. He listed three main pathways: direct, lymphatic and hematogenous. Wangenstein found that in 25 per cent of those cases coming to autopsy, the disease was confined to the stomach and to the adjacent nodes. This is a good argument in favor of radical surgery. The following reports were made on the incidence of positive lymph nodes in resected specimens: Roscoe Graham 67 per cent, Lahey 87 per cent, Mayo 72 per cent and Memorial Hospital 62 per cent. However, in a thorough study of 44 specimens of total gastrectomy in which at the time of operation the lesion was thought grossly to be favorable for cure, Ransom found no malignant change at either the esophageal or duodenal end in but 17; both ends were positive in 7; the esophageal end only in 14, and the duodenal end only in 6. Of the 46 cases studied, he detected positive regional lymph nodes in 36.

Diagnostic errors determined at operation were found in 10 to 20 per cent. Ransom found that 10 per cent of those lesions called benign at operation proved to be malignant in the pathologic laboratory. Welch reported a 14 per cent error and Moore a 15 to 20 per cent error. Engel<sup>128</sup> reported an 18 per cent diagnostic error by roentgenologic examination, 17 per cent error by gastroscopy and an 8 per cent error when both methods were employed. When a lesion was known to be present, the error in differentiation of ulcer and carcinoma was 34 per cent for the roentgen ray, 20 per cent for the gastroscope, and 14 per cent for the combined instruments. Engel, furthermore, has discovered that there is an early loss of desire for meat as well as the presence of fatigue, indigestion, loss of appetite and discomfort before and after eating. Combined with this was the finding that 56 per cent of patients with gastric carcinoma have a serum protein level below 6 gm. per 100 cc. Welch found the technic of Papanicolaou in 47 smears to be positive in 14 cases of 22 proved malignancies and to be negative in 24 cases all of which were proved benign. Sussman and Lipsay<sup>129</sup> expressed the opinion that roentgenologic differentia-

tion is not always unequivocal. A niche that projects from a rigid indentation or a depression into the gastric contour makes them very suspicious of malignant disease.

The question of an ulcer undergoing malignant degeneration has proponents for both viewpoints. Klein<sup>130</sup> was of the opinion that 2 to 5 per cent of peptic ulcers of the stomach become malignant. Abrahamson and Hinton<sup>131</sup> found that 11.5 per cent of patients have a history that makes this possibility a factor for consideration. They hold to the idea that the development of malignant change is more closely related to the chronic pathologic involutionary changes, which take place in the gastric mucosa, than to the benign peptic ulceration itself. Ransom made the statement that 17 of 19 cases revealed a carcinoma to develop on an old ulcer. Ogilvie quoted Maingot's figure of 10 per cent of ulcers becoming malignant. Then he said, "In twenty years of gastric surgery I have never seen a gastric ulcer become malignant. I feel that Maingot's experience is a piece of unparalleled bad luck in the practice of an otherwise very lucky man," and "An ulcer in the bucket has never been known to become malignant."

Many warn that a malignant lesion may apparently heal under a medical regimen as if it were a benign ulcer. Walters found this to be so in 80 per cent and Engel in 81 per cent of cases.

Coexistent duodenal ulcer and gastric malignant disease was reported by Fischer, Clagett, and McDonald<sup>132</sup> who collected 48 cases with a five-year cure in 12; 22 died of the malignancy. Dixon and Weismann<sup>133</sup> culled the literature and reported one patient treated by total gastrectomy. Yarnis<sup>134</sup> presented 3 cases. These patients usually have a higher survival rate probably because of an earlier diagnosis. But in a high percentage at the time of operation the duodenal ulcer was inactive or healed.

As stated previously, the surgical treatment of gastric carcinoma revealed a definite trend toward total gastrectomy. Taylor<sup>135</sup>, an Englishman, wrote, "If there is no widespread metastases, the surgeon should be prepared to remove the whole stomach, together with the omentum, the spleen, the transverse colon and the tail or body of the pancreas, if these are involved." Longmire<sup>136</sup>, combining the reports of Horsley, Farris, Ransom and Colles, and Jones and Kehm with his own, concluded that these lead to the belief that the operability rate and percentage of five-year cures following surgical treatment of malignant gastric neoplasms would be increased if total gastrectomy were more often employed even in the treatment of the smaller, early lesions of the pylorus and fundus.

Despite this trend to total gastrectomy, most series reported had as a curative operation a preponderance of partial resections. Operability rates varied from 36.7 per cent at Bellevue as reported by Abrahamson and Hinton, to 79 per cent by Pack<sup>137, 138</sup>. Wangenstein contrasted an operability rate of 57

per cent in 1936 with 88 per cent in 1945. Of those patients seen by Engel with a preoperative diagnosis of malignancy 48 per cent had inoperable lesions. The frequency of exploration and biopsy procedures was reported by Engel as 36 per cent with a 0.2 per cent mortality; Marshall and Welch<sup>139</sup> 45.7 per cent with a 5 per cent mortality; Wangensteen 14.5 per cent with an 8.2 per cent mortality, and the Bellevue group a 15.5 per cent incidence. Percentages of resections, both total and subtotal, were as follows: Engel 18 per cent for curative resections; Marshall and Welch 41 per cent; Wangensteen 52.2 per cent; Abrahamson and Hinton 13.7 per cent; Eliason 35 per cent and Pack 35 per cent. Abrahamson and Hinton had a 62.3 per cent mortality for gastric resection for the years 1939 to 1945; other figures were Pack 12.2 per cent; Marshall and Welch 11.5 per cent; Wangensteen 16.6 per cent with a 4.9 per cent rate in 1945, and Engel a 2.8 per cent mortality rate for presumably curative subtotal resections.

Palliative operations were thought to be worth while especially by Wangensteen. He found that people subjected to resection, the only procedure he feels to be of value, lived an average of 22.4 months. The average survival of those with liver metastases following a palliative resection was fifteen months. Cheevers reported that only 9.2 per cent of patients untreated lived over six months and 40 per cent of all untreated patients were dead within six months of the onset of symptoms. Engel reported that in 18 per cent of his series he did a palliative operation whereas Marshall and Welch did such in 13 per cent, with a 19 per cent mortality.

Mortality for total gastrectomy is becoming much lower. Wangensteen and Pack reported 30 per cent, but now the Mayo group report a figure of 16.6 per cent, Engel 18 per cent and Lahey 10.7 per cent since 1942. Percentages of survivors of total gastrectomy living for five years were reported by Wangensteen to be 10 and by Pack to be 18.3 (this represents a 6.6 per cent five-year survival of patients subjected to resection in Wangensteen's series). Welch believes that 5 per cent should represent the five-year survival rate in gastric carcinoma when positive nodes are found and 50 per cent when no metastases are found. Jennings<sup>140</sup> rightfully emphasized the fact that ten-year survival of patients over 60 is not 100 per cent. Pack had a 13.7 per cent three-year survival rate for those with carcinoma and without nodes. Ransom had 3 of 41 patients with carcinoma living over five years. Of those surviving resection, Wangensteen had 21.5 per cent and Pack 34.7 per cent living after five years. Lahey estimated that if operation is survived then 50 per cent have a chance of living twelve months; 28 per cent eighteen months; 16 per cent twenty-four months, and 9 per cent thirty-six months.

Technical advances were of minor significance. Orr<sup>141</sup> depicted a new method of anastomosis utilizing the "Roux en Y" procedure. Garlock<sup>142</sup> does this same opera-



tion through a combined abdominothoracic incision. Orr divided the jejunum 15 cm. below the ligament of Treitz. A retrocolic end-to-side esophagojejunostomy to the distal jejunum and an end-to-side jejunojejunostomy between the proximal cut end of the jejunum and the bowel descending from the esophagus completed the operation. Wahren<sup>143</sup> preserved the ascending branch of the left gastric, for it nourishes the lower end of the esophagus. All employ Lahey's maneuver of peritoneal flaps from the diaphragm to support the esophagojejunostomy. Marshall, Orr, Pack, Wangenstein, Garlock and Ransom outlined their respective procedures. Enterenterostomies are preferred by Lahey, Wahren, Marshall,<sup>144</sup> Smithwick<sup>145</sup> and Pack,<sup>138</sup> but not by Longmire. Ransom<sup>146</sup> reported 30 done and 27 not done, and Mayo 46 done and 31 not done. In Ransom's series, feeding jejunostomy was performed in 49 and omitted in 11 cases. Longmire does not do it and Pack who did it formerly now omits this procedure. Garlock<sup>142</sup> prefers it. Splenectomy apparently is not routine—Ransom reported 24 done and 36 not done. We believe that routine splenectomy as suggested by Dr. Lahey is not only desirable but greatly facilitates mobilization of the stomach in total gastrectomy. Hume and Guy Blackburn<sup>147</sup> described a gastrectomy performed synchronously by an abdominal and a thoracic surgical team. Harper<sup>148</sup> outlined his combined thoraco-abdominal approach through the bed of the ninth rib, across the costal arch and down along the left border of the right rectus. Garlock does a left lateral rectus incision first to explore the abdomen. If the lesion is favorable, he opens the chest by cutting the costal cage and going through the eighth interspace. Antecolic and retrocolic types have proponents equally vehement, as do closed and open types of anastomoses. Peritonitis and pulmonary complications were the most frequent causes of operative deaths. Almost all used postoperative Wangenstein suction for from three to five or more days. Pack used 3 cc. of eucupine into the area of the sixth to the eleventh thoracic nerves in the postaxillary line for the postoperative relief of pain. Many have the patients ambulatory in forty-eight hours. Several left subphrenic abscesses following total gastrectomy were reported. For high lesions Humphreys and Garlock preferred to carry out total resections as then they have no difficulty with postoperative retention owing to pylorospasm.

MacDonald, Ingelfinger, and Belding<sup>149</sup> studied 2 patients who had survived total gastrectomy for ten and three years respectively, and another patient who had had a total gastrectomy, splenectomy and partial pancreatectomy five years previously. The cases in which only gastrectomy had been done had normal pancreatic enzymes with good fat absorption on low fat diets. Their vitamin "A" tolerance curves were normal except for delayed absorption. Following meals they had an early and marked hyperglycemia which was transient. In the case with splenectomy and partial pancreatectomy, there was a deficiency of pancreatic enzymes, deficient fat absorption, flat vitamin "A" tolerance curve, and postcibal hyperglycemia which was sustained. Two of the 3 patients developed a macrocytic hyperchromic anemia after two and five years postoperatively; the other patient received liver prophylactically. In a review of all cases reported they found a very high incidence of this type of anemia. It developed in three or more years after total gastrectomy.

Fairchild and Shorter<sup>150</sup> presented an interesting approach to gastric carcinoma. They administered heavy dosages of irradiation directly onto the stomach and cancerous tissue through the opened abdomen. Of 32 patients, 15 were treated by direct irradiation. In 8 the disease appeared to be limited to an area feasible for treatment. Of these, 1 patient lived twenty-four months, 2 fifteen months and the others survived a shorter period of time.

Maquire and Mitchell<sup>151</sup> reported that the aorta was perforated by acid gastric contents following a transthoracic partial gastrectomy for carcinoma. For this reason, they proposed an esophagojejunostomy rather than an esophagogastrostomy. A leaking anastomosis is hazardous regardless of the components.

#### MISCELLANEOUS ENTITIES

Congenital hypertrophic pyloric stenosis in 147 cases was reported by Akin and Forbes<sup>152</sup>; 81.7 per cent were males and over 50 per cent were first born. The mortality was 5.4 per cent, with an operative mortality of 2.8 per cent; 76 per cent had a palpable tumor. They gave hydrochloric acid intravenously as well as inhalations of 30 per cent carbon dioxide to raise the hydrogen ion concentration of the blood. Open drop ether was the preferred anesthetic agent. The duodenum was opened twelve times in 143 cases. Bendix and Necheles<sup>153</sup> studied 20 adults who had had this condition in childhood. They found no immediate or late undesirable effects of the Ramstedt operation. In these patients and their families there was a high incidence of nervous imbalance. In later life 18 per cent developed ulcer or an ulcer syndrome, 41 per cent were underweight, and 77 per cent were of unstable nervous temperament. They proposed the theory that the etiology of the hypertrophy was an autonomic imbalance plus local irritation during embryonic life.

Acute volvulus of the stomach in the longitudinal axis with occlusion of the cardia was described by Silvestre-Begniss and Torres<sup>154</sup> in a 29-year-old woman who had rheumatic heart disease. The basis of this they found to be a congenital defect with a lack of peritoneal coalescence and the characteristics of a "mesenterium communis."

Rosenthal, Frost and Thompson<sup>155</sup> recorded a death due to chronic and acute gastric dilatation forty days after ileostomy and colostomy for ulcerative colitis. This they attributed to sympathetic stimulation plus some duodenal obstruction, which they believed vagotomy might have abolished. Reduction of coronary blood flow by the acute dilatation they reasoned played a role in the death. Apropos of dilatation, Leger and Maes<sup>156</sup> reported 30 cases of spontaneous rupture of the stomach. This fatal accident—the longest survival was thirty-five hours—occurred with equal frequency in both sexes with all patients between the ages of 11 and 30 years. One patient presented a history of drinking beer and then of taking soda bicarbonate.

Three unusual types of gastritis were described: giant hypertrophic gastritis, emphysematous gastritis, and acute phlegmonous gastritis. Maimon<sup>157</sup> and his co-workers, in a large series of gastroscopic examinations, found an incidence of 0.17 per cent of giant hypertrophic gastritis. The importance is in its differentiation

from a neoplastic process. Welch and Jones<sup>158</sup> described emphysematous gastritis as an infection characterized by the presence of numerous small gas bubbles throughout the stomach wall. The organisms cultured were *B. coli*, a few nonhemolytic streptococci, and a few *Staphylococcus aureus*. Treatment was supportive with the administration of both penicillin and sulfadiazine. This pathologic entity they differentiated from a solitary cyst of gas in a bowel wall, "cystic pneumatosis," which is uncommon in the stomach and tends to disappear spontaneously, and also from "phlegmonous gastritis," which displays no intramural gas but often follows chemical or mechanical trauma. The latter has a 50 per cent mortality. Guzzetta and Southwick<sup>159</sup> discussed this last mentioned entity in reporting a case that followed measles. Their patient, who recovered, was treated with penicillin, sulfadiazine and gastrotomy. Of the 335 cases reported in the literature, with a sex ratio of 3 males to 1 female, 70 per cent were infected with hemolytic streptococci. They recounted the previous mortality as 84 to 92 per cent.

Nicolo<sup>160</sup> did a saddle resection with longitudinal suture of the lesser curvature for a tuberculous ulcerocicatrical type of lesion in a 52-year-old man who had previously had a gastroenterostomy. He remarked that the usual tuberculous lesion is situated in the pyloric or juxtapyloric area. Warriner Woodruff, of Saranac Lake, New York, and one of us (E.S.P.) operated on a man with an open tuberculous chest lesion who presented the clinical picture of pyloric obstruction. This patient had had a gastroenterostomy for an ulcer before he developed tuberculosis. A few months previous to the development of obstructing symptoms he had had a perforated ulcer in the region of the anastomosis. At that time the perforation was closed and the gastroenterostomy was disconnected. At the last operation a large perforated ulcer with a proximally adjacent tuberculoma was found on the lesser curvature in the prepyloric area. There was as well a generalized tuberculous peritonitis. The perforation had been sealed spontaneously by the gastrohepatic omentum. Operation consisted of resection of the involved area of the stomach and first part of the duodenum with an end-to-end duodenogastrostomy. This was effected by tucking the larger gastric end into the duodenum as proposed by von Haberer and as in the Mayo subtotal resection. The patient made an uneventful recovery although the pulmonary tuberculosis continues.

Gastro-esophageal resection and total gastrectomy were performed by Phemister and Humphreys<sup>161</sup> for bleeding esophageal varices in Banti's syndrome. The trans-thoracic esophagogastrrectomy, which included the lower  $3\frac{1}{2}$  inches (8.75 cm.) of the esophagus and the upper 2 inches (5 cm.) of the stomach, was performed on an 18-year-old patient who had a hyaline thrombus in the splenic vein. Three and one-half months after operation the patient was still well. The total gastrectomy, also done on an 18-year-old, resulted in the patient having but two episodes of bleeding in the thirty-two months following operation. Wangenstein, in commenting on this, revealed that he had done 90 to 95 per cent resections on 3 patients, 2 of whom were still living.

Duodenal regurgitation into the stomach owing to the obstruction of the duodenum by the superior mesenteric vessels was found by Metz<sup>162</sup> in 0.5 per cent of all his

gastrointestinal series. The symptoms of postcibal fullness, right upper quadrant distress, nausea, vomiting and weight loss he believed could be corrected by either medical or surgical means. Medical measures were concerned with weight gain and postural changes. Surgical measures proposed were either a gastroenterostomy with a string about the pylorus to occlude it or a duodenojejunosomy 6 cm. to 8 cm. distal to the pylorus.

Kenamore<sup>163</sup> was able to recover without laparotomy a bobby pin from a child's stomach by the use of an alnico magnet attached to a stomach tube. This would be a good stratagem as long as a gastric or an esophageal perforation did not occur unknowingly.

Three papers dealt with isolated surgical conditions. Davis and Salkin<sup>164</sup> reported a congenital intrathoracic mediastinal cyst which was of gastric origin. This was the twenty-sixth such case in the literature. Nine had been found at autopsy and of the 17 in which operation had been performed, 10 had been successful. These cysts are usually located paravertebrally in the posterior mediastinum. They expand retropleurally more often into the right hemithorax—18 were right and 5 left. In 7 of the cases an ulcer was also present. Incarceration of the stomach in an umbilical hernia caused a weight loss from 285 pounds to 95 pounds. The hernia was repaired by Orr<sup>165</sup> and the patient regained weight to 243 pounds. Sommer and Mills<sup>166</sup> reported an unusual complication following a crush injury of the chest. Apparently during one of the aspirations of the pneumohemothorax of the left chest subsequent to the accident, the needle was inserted into the stomach. This organ had gained entrance into the chest through a diaphragmatic hernia produced at the time of the accident. This eventuated in a thoracogastric fistula and a multilocular empyema complicating the diaphragmatic hernia. As a result of their experience they advised, in addition to normal corrective procedures, decortication of the lung with the insertion of multiple drainage tubes into the chest.

Some interesting observations of the effects of heavy dose irradiation to the stomach were made by Brick<sup>167</sup>, Bowers<sup>168</sup> and by Hamilton<sup>169</sup>. These observations were made largely on patients receiving therapeutic doses for retroperitoneal nodes metastatic from primary testicular tumors. Bowers and Brick reported 3 antral portion perforations, 3 cases of hemorrhages, and in some, jejunal injury. Six patients subsequently required surgical intervention. In one of these, impaired healing of the duodenal stump was noted. Fifty per cent of the patients (128 out of 256) developed epigastric distress in two to three months and 35 developed a large single gastric ulcer. Most ulcers were on the posterior antral wall. Other changes noted were a rigid antrum with a patulous pylorus, an atrophic mucosa with a pyloric ulcer in 1 case, generalized increased fibrosis and vascularity intra-abdominally with the omentum appearing as a small shred of tissue and shortening of the mesentery of the colon and jejunum. Since deleterious effects on the stomach can be obtained by this agent because the individual response is variable, and since the result of radiation is too difficult to predict, Brick concluded that radiation has no place in the treatment of peptic ulcer. Although it is true his dosage was considerably larger, he could not confirm the depression of acidity as reported by Palmer and Templeton.

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## FLEXI-RIGID, OPTICAL EOSPHAGOSCOPE

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Esophagoscopy, as is usually practiced today, has certain inherent dangers and disadvantages. The introduction of an open end rigid esophagoscope into the hypopharynx and esophageal orifice is uncomfortable, and not without danger of producing abrasions and tears that open avenues for infection into the mediastinum. It is technically more difficult for the operator than the passing of a flexible instrument. The visual field without the aid of optics is distant and small, adding to the difficulty of interpretation.

Esophagoscopy, generally, is in about the same relative position to clinical esophageal exploration as was gastroscopy with the rigid gastroscope before Wolf and Schindler<sup>1, 2</sup> introduced the flexible gastroscope in 1932.

The endoscopically inclined gastroenterologist, is interested in lesions affecting the esophagus as well as those of the stomach. There are many expertly trained in the field of gastroscopy who hesitate to use the rigid esophagoscope because of its hazards.

Rigid instruments for both gastroscopy and esophagoscopy using flexible rubber tipped obturators are not new and have been described by Schindler<sup>3</sup> who also quotes Hubner, Henning, and Jackson. While such an obturator is of distinct value and improvement over the open end tube scope, it still does not permit the flexibility for passing that was hoped for.

Since 1943 I planned several types of flexible optical scopes and different types of obturators for rigid scopes and had them made by a manufacturer of gastroscopes. Of the various types or models the most practical of all was evolved this year. It is passed in the same way, and with the same ease as the flexible gastroscope.

A standard Jackson type of esophagoscope with an inside diameter of 9 mm. is fitted with a flexible stainless steel spiral protruding 6 inches beyond the open end of scope and tipped with a flexible pointed rubber finger, such as that used in a flexible gastroscope (See Figure 2). The flexible spiral is attached to a solid metal base which fills the beveled end of the scope. This is attached to a solid metal rod the length of scope and meets a metal cork at the proximal end, firmly securing the protruding flexible portion during passage of the scope (See Figure 1). Once the scope is passed to the desired depth the flexible obturator is withdrawn and the optical tube of the Eder Flexi-Rigid gastroscope, encased in a metal sheath (See Figure 1) of about  $\frac{3}{4}$  the length of scope, is passed to the desired focal depth. The metal sheath is retained in the same position throughout the examination, secured by friction at the

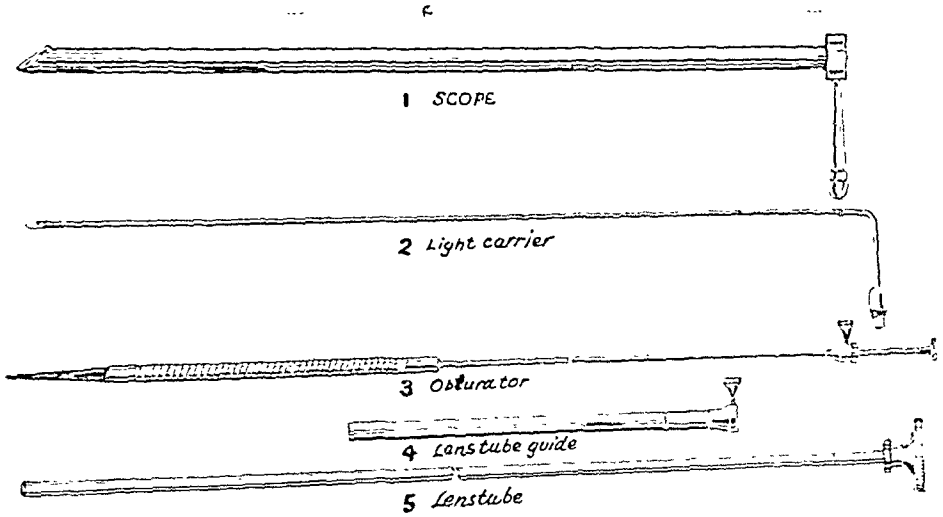


FIG. 1. SHOWS THE COMPONENT PARTS OF THE ESOPHAGOSCOPE SEPARATELY

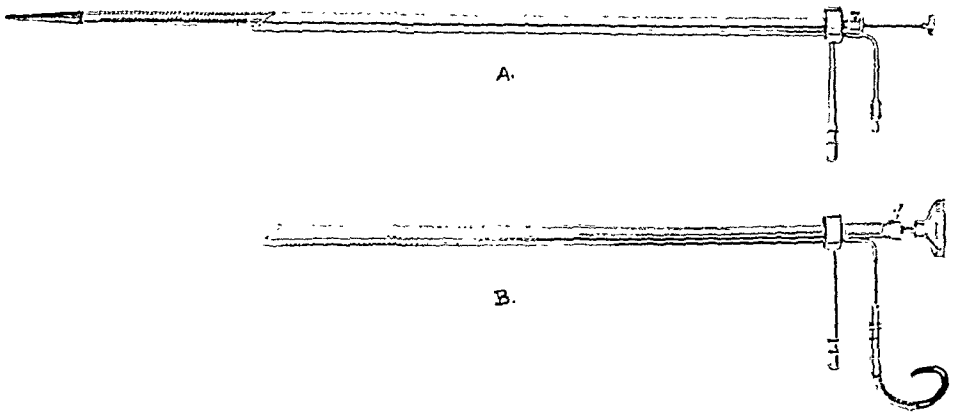


FIG. 2

A. Shows the scope completely assembled and ready for passing into the esophagus.  
B. The same scope with the flexible obturator removed and the lens tube held in place at the proper focal length by the lens tube guide ready for viewing the esophagus.

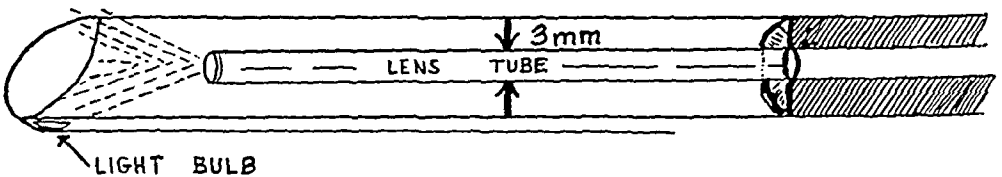


FIG. 3. Diagrammatic drawing to show more accurately the position of the objective in reference to the open end of the scope. It allows sufficient area of visualization, and it cannot be obstructed by folds of the esophageal mucosa.

proximal end of scope, and by means of a small set screw allows for adjustment of the optical tube to the proper focal distance and keeps it centered at all times.

The optical system allows magnification of  $8\times$  the image as ordinarily viewed through the rigid scope, and can be used in any standard rigid esophagoscope 7 to 10 mm. internal diameter by varying the size of the retaining sheath.

The advantages of this modification for the standard esophagoscope are:

1. Safer and easier introduction of the scope with the same technique and position as in gastroscopy with the flexible gastroscopy.
2. Allows magnification of  $8\times$  the image viewed through the rigid scope with unaided eye.
3. The objective is protected from mucous and the mucosa by the end of the scope.
4. For purpose of medication, suction or cutting biopsy, the optical system and sheath can be removed and replaced at will.
5. Endoscopy of the esophagus will grow in interest to those qualified in gastroscopy.

NOTE: This work was done in collaboration with Mr. Ludwig Streifeneder, of Eder Instrument Company, Chicago, Illinois.

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## THE QUANTITY AND COMPOSITION OF HUMAN COLONIC FLATUS

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### INTRODUCTION

The first analyses of the intestinal gas in human subjects date back to the beginning of the nineteenth century when Magendie<sup>1</sup> (1816) was able to demonstrate the presence of carbon dioxide, methane and nitrogen in samples of gas obtained from the intestinal tract of newly executed individuals. In a more extensive publication in 1862 Ruge<sup>2</sup> in Vienna reported on the composition of flatus collected from three normal subjects, and Schmidt<sup>3, 4</sup> in 1898 gave detailed results of analyses from one individual. In recent years studies on the composition of the colonic gas have been published by Andersen and Ringsted<sup>5</sup> (1943). A summarized survey of these findings is given in Table 1 for comparative purposes.

While the above mentioned investigations only include analyses of individual samples of human flatus, two publications are available in the literature in which the excreted amount of colonic gas has been measured. Thus Fries<sup>6</sup> in 1906 in a single experiment noted a flatus excretion of about 1 liter daily, and Beazell and Ivy<sup>7</sup> in 1940 in an investigation of 5 normal subjects found an average 24-hour excretion of 524 ml. In the latter experiments, however, the gas was collected in rubber bags attached to the back of the individuals, and it seems likely, as also stated by the authors, that some diffusion of air from the container has taken place under these circumstances. This leaves the single experiment performed by Fries in 1906 as the only reliable analysis including a determination of both the composition and 24-hour quantity of excreted human flatus.

The present investigation was carried out in Denmark during the period from 1943 to 1947 with the purpose of procuring a large series of quantitative and qualitative data on the human flatus excretion. A report on this study together with a summary of the existing literature concerning the intestinal gas and colonic flatus under normal and pathological conditions was published as a monograph by the author in 1947<sup>8</sup>. The data presented in this paper will be limited to a description of the technique of flatus collection and analysis with a brief survey of the analytical findings.

### TECHNIQUE FOR FLATUS COLLECTION AND ANALYSIS

During the periods of flatus collection the individuals were confined to bed. A thin rubber catheter was inserted in the rectum and connected with a rubber

tube which was carried forward along the genito-femoral fold and fixed to the inguinal region by means of adhesive tape. The rubber tube was connected with a gas collecting apparatus, contained in a cabinet placed next to the bed, the tube entering the cabinet through a hole in the back wall at the level of the mattress in the bed. The discreet installation of the collecting apparatus in a locked cabinet was thought to be the chief reason why the flatus collecting never met with any objections from the side of the individuals. Only an occasional experiment had to be discontinued on account of obstruction of the rectal catheter by fecal masses. Except in the case of patients suffering from hemorrhoids the anal sphincter provided a tight closure around the catheter. This fact was demonstrated by the absence of leakage in the system, which would have been made apparent by constant bubbling of air through the solution in the collecting chamber, as contrasted to the periodic emissions of colonic flatus.

TABLE 1

*Survey of previous studies on the composition of human colonic flatus*

	YEAR	NUMBER OF INDIVIDUALS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>
			%	%	%	%	%
Ruge, E. ....	1862	3	25.4	0.0	30.0	8.1	36.5
Schmidt, A. ....	1898	1	12.5	3.2	4.7	44.0	35.6
Fries, J. A. ....	1906	1	10.3	0.7	29.6	0.0	59.4
Andersen, K. ....	1943	6	9.8	1.2	0.9	5.5	82.7

The collecting apparatus, reproduced in Figure 1, consisted of a small absorption flask A, a collecting chamber B, and a leveling bulb C. During the experiments the leveling bulb was placed at a level lower than B, thus providing the suction in the system.

The flatus first bubbles through A, which contains 10 ml. of a 2 per cent cadmium acetate solution in 2 per cent acetic acid. This solution absorbs the hydrogen sulphide quantitatively and at the same time serves as a water trap. The absorption flask is provided with 2 ground glass cocks which permit the convenient connection and disconnection between the rectal catheter and the apparatus.

The graduated chamber B, in which the flatus is collected during the experiment, has a capacity of about 1500 ml. and is at the beginning of the experiment filled with a saturated solution of calcium chloride of a specific gravity of 1.40, in which solution the absorption of carbon dioxide is only  $\frac{1}{16}$  of that in water. At the end of the experimental period the amount of gas in B is measured by placing the surface of the solution in the leveling bulb at the

level of the solution in B. After measuring the gas volume, portions of the flatus are transferred for storage to Hempel pipettes filled with mercury or saturated calcium chloride solution. The glass stopcock and the glass cup attached to the top of the chamber serve for the transfer. During this the stopcock between A and B is closed, and the leveling bulb C is lifted to produce a positive pressure in B.

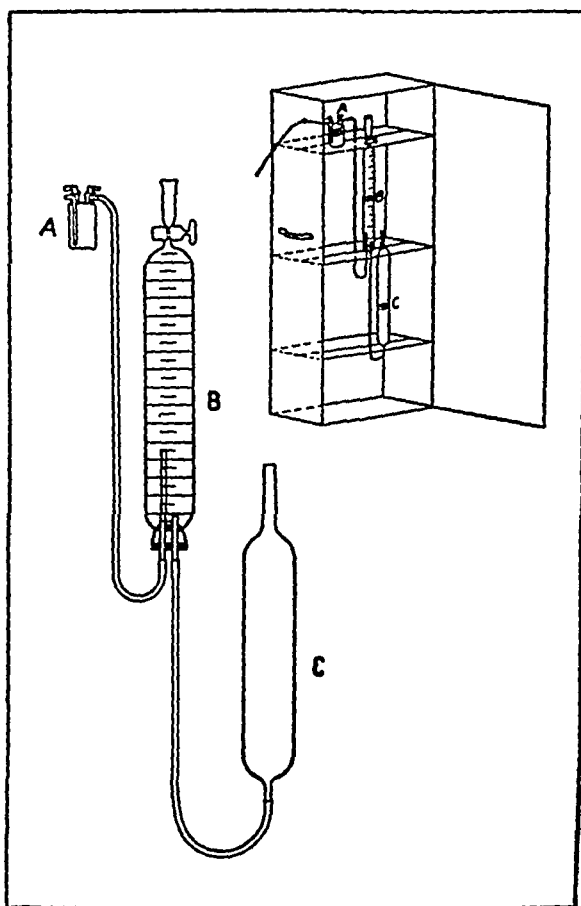


FIG. 1. APPARATUS FOR QUANTITATIVE COLLECTION OF FLATUS

All flatus samples were analyzed for carbon dioxide, oxygen, methane and hydrogen, the analyses being performed by the Van Slyke manometric apparatus. The carbon dioxide and oxygen contents were first determined on a separate sample by the method of Van Slyke and Sendroy<sup>9</sup>. Another sample of flatus served for determination of the combustible gases hydrogen and methane. The hydrogen determination was performed as described by Van Slyke and Hanke<sup>10</sup>. A special combustion chamber was attached to the extraction chamber of the Van Slyke apparatus, after which a known amount

of pure oxygen was introduced into the combustion chamber and the gas mixture brought to combustion under reduced pressure by means of a heated platinum wire. After the combustion, which usually took place under explosion, the gas was transferred to the extraction chamber of the Van Slyke apparatus and the reduction in volume noted.

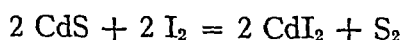
In order to estimate both the hydrogen and methane content it was necessary to determine also the amount of carbon dioxide formed by the combustion. This was accomplished simply by analyzing the sample transferred to the Van Slyke apparatus from the combustion chamber for carbon dioxide (by the method of Van Slyke and Sendroy) and from this value subtract the original carbon dioxide content of the flatus sample. The amount of carbon dioxide formed by the combustion is equivalent to the amount of methane present in the sample. The hydrogen content of the sample could then be calculated according to the following formula:

$$\text{Hydrogen percentage} = \text{Observed reduction in gas volume following the combustion} \times 0.67 - \text{Methane percentage} \times 1.33$$

The nitrogen content was calculated by subtracting the carbon dioxide, oxygen, methane and hydrogen percentages from 100.

In the calculations the values found were corrected for the volume of atmospheric air contained in the rectal catheter, rubber tubing and above the fluid in the absorption flask A. Duplicate analyses of all the gases could usually be performed in about 45 minutes.

The hydrogen sulphide excreted during the experiment was determined according to Quitmann<sup>11</sup> in aliquots of the cadmium acetate solution in the absorption flask A. The efficacy of this solution for hydrogen sulphide absorption was proved by testing the calcium chloride solution in the collecting chamber B for hydrogen sulphide. Such tests always turned out to be negative. The hydrogen sulphide by passing through the cadmium acetate solution is converted to cadmium sulphide. The amount of cadmium sulphide formed is determined by adding a known amount of iodine in potassium iodide solution. The sulphide reacts quantitatively with the free iodine according to the equation:



The amount of iodine used in the reaction can be estimated by titration of the residual iodine with sodium thiosulfate. The method permits the determination of very small amounts of hydrogen sulphide. Thus in the titration 0.1 ml. of 0.005 n sodium thiosulfate corresponds to 0.0085 mg. hydrogen sulphide, or 0.0050 ml. hydrogen sulphide.

A hydrogen sulphide analysis may be completed in a few minutes.

## THE QUANTITY AND COMPOSITION OF COLONIC FLATUS IN NORMAL INDIVIDUALS

a. *Values observed on an ordinary (cabbage free) diet*

Measurements of the quantity of flatus excreted on an ordinary diet were carried out on 20 normal individuals<sup>12</sup> using two 5 hour periods of collection (9 a.m. to 2 p.m., and 5 p.m. to 10 p.m.). In the experiments No. 1, 2, 4, 5, and 7, however, the flatus collecting was performed during the night. The results of the analyses are reproduced in Table 2, which shows that the amount of flatus excreted varies greatly in different individuals with an average value of 1.48 ml. per minute. It appears probable that this figure is somewhat higher than the value for the spontaneous flatus excretion, as the presence of the catheter in the rectum may have conditioned an increased peristalsis. Also, the rather high bran content of the bread during the war and in the post-war period in Denmark may have tended to increase the formation of intestinal gas.

The size of the individual emissions of flatus usually varied between 25 and 100 ml. The gas excretion as a rule was livelier after the meals than in the intermittent periods. Thus in one experiment in which special notes were kept on the time of emissions it was observed that after the intake of dinner at 1 p.m. passage of gas took place at 1:20, 1:23, 1:30, 1:34, 1:37, 1:39, 1:55, 2:05, 2:08, 2:17, 2:29, 2:40, 2:57, 3:07, 3:20, 3:50, 4:30, and 5:05 p.m. This means that during the first hour after the meal emission of flatus occurred 10 times, during the second one hour period, 5 times, during the third hour once, and during the fourth hour 2 times. While, therefore, the excretion of flatus may take place 8-10 times during a one-hour period, the interval between emissions may on other occasions be as great as one and one half hours.

All the flatus samples entered in Table 2 were found to contain carbon dioxide, hydrogen and nitrogen, most of the samples oxygen, whereas methane and hydrogen sulphide were occasionally lacking. It should be noted that the concentration of carbon dioxide is frequently higher than corresponding to the tension of this gas in the tissues, a fact which is indicative of the great intensity of the fermentative processes in the colon. It is further seen that the content of the combustible gases is often considerable, the average values for hydrogen and methane being 20.9 and 7.2 per cent respectively. However, even with a flatus excretion of about 2 liters in 24 hours the caloric value of these gases will correspond to a loss of only about 0.1 to 0.2 per cent of the caloric value of the ingested food as compared to a similar loss in the cattle of 10-15 per cent of the nutritional value of the feed.

In contrast to the popular assumption the hydrogen sulphide content of the colonic gas was found to be very low, the concentration being of the magnitude 0.0001 to 0.001 per cent, or a few mg. per cubic meter of flatus. It is

of interest to compare these values with the figures given in textbooks on hygiene concerning the recognition of hydrogen sulphide through its smell. Thus it is stated that the presence of 0.8 mg. of this gas in 1 cubic meter of air gives a recognizable smell, whereas a content of 5 mg. per cubic meter yields a very strong smell.\* This comparison shows that the hydrogen sulphide present in the flatus, in spite of its low concentration will frequently be noticeable as a definite odor.

TABLE 2

*The quantity and composition of colonic flatus in 20 normal individuals on an ordinary, cabbage free diet*

EXPERIMENT NO.	MIN.	FLATUS	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
		ml.	ml./min.	%	%	%	%	%	%	ml./cu. m.
1	240	420	1.75	9.6	0.0	8.1	32.0	50.3		
2	300	535	1.78	11.6	4.0	9.3	27.8	47.3		
3	720	590	0.82	7.9	6.5	7.9	26.9	50.8		
4	720	605	0.84	11.7	1.0	30.3	17.3	39.7		
5	420	255	0.61	1.2	3.5	20.0	24.6	50.7		
6	375	840	2.24	8.3	1.3	0.0	19.1	71.3		
7	300	310	1.03	5.8	1.3	9.3	22.6	61.0	0.00170	26
8	440	455	1.03	15.0	0.3	0.0	34.0	50.7	0.00079	12
9	600	650	1.09	14.4	0.0	2.3	24.4	58.9		
10	600	215	0.36	5.4	2.3	0.0	3.1	88.2	0.00000	0
11	600	1070	1.79	13.8	0.8	0.0	31.4	54.0	0.00000	0
12	490	1340	2.74	13.7	0.7	0.0	17.4	68.2	0.00080	12
13	600	648	1.08	13.3	8.5	0.0	30.1	48.1	0.00000	0
14	600	425	0.71	7.1	1.5	27.3	7.1	57.0	0.00000	0
15	600	750	1.25	7.5	3.8	10.2	17.0	61.5	0.00015	2
16	340	1350	3.97	4.7	15.7	0.6	6.3	72.7	0.00012	2
17	600	985	1.64	6.0	10.7	0.0	18.1	65.2	0.00000	0
18	600	490	0.82	7.7	4.4	0.0	30.1	57.8	0.00000	0
19	600	1200	2.00	6.5	8.3	2.3	7.6	75.3	0.00000	0
20	600	1250	2.08	8.9	4.0	16.6	10.7	59.8	0.00005	1
Average.....			1.48	9.0	3.9	7.2	20.9	59.0	0.00028	5

The values for the flatus excretion reported in Table 2, on a cabbage free diet, agree well with values observed in 25 subjects on a cabbage free and milk free diet during the period 1945-1946. The summarized figures for these series of study are presented in Table 3. The individual values for the latter group may be found in Tables 5 and 6.

#### *b. The effect of intake of brussel sprouts*

As the ingestion of cabbage is generally assumed to cause an increased excretion of flatus this problem was made the subject of a special study<sup>12</sup>. Thus

\* The toxic effect of hydrogen sulphide on inhalation starts with a concentration of 100 to 150 mg. per cubic meter of air.

TABLE 3

*Summarized survey of the quantity and composition of colonic flatus in normal individuals*

PERIOD	NUMBER OF INDIVIDUALS	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
		ml./min.	%	%	%	%	%	%	mg./cu. m.
1943-44*	20	1.48	9.0	3.9	7.2	20.9	59.0	0.00030	5
1945-46†	25	1.45	9.7	5.5	3.1	12.0	69.7	0.00010	2

\*Ordinary diet, cabbage free.

†Ordinary diet, cabbage free and milk free.

TABLE 4

*The quantity and composition of colonic flatus in 12 normal individuals on an ordinary diet before (a) and after (b) intake of brussel sprouts*

EXPERIMENT NO.	MIN.	FLATUS	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
		ml.	ml./min.	%	%	%	%	%	%	mg./cu. m.
8a	440	455	1.03	15.0	0.3	0.0	34.0	50.7	0.00079	12
8b	500	1255	2.50	16.8	8.0	0.0	12.3	62.9		
9a	600	650	1.09	14.4	0.0	2.3	24.4	58.9		
9b	600	950	1.58	21.0	0.9	0.0	18.3	59.8	0.00023	4
10a	600	215	0.36	5.4	2.3	0.0	3.1	88.2	0.00000	0
10b	600	230	0.38	5.5	0.0	0.0	8.3	86.2	0.00000	0
11a	600	1070	1.79	13.8	0.8	0.0	31.4	54.0	0.00000	0
11b	495	1200	2.43	17.5	0.6	0.0	38.3	43.6	0.00000	0
12a	490	1340	2.74	13.7	0.7	0.0	17.4	68.2	0.00080	12
12b	300	1240	4.14	3.6	14.5	0.0	2.3	79.6	0.00090	13
13a	600	648	1.08	13.3	8.5	0.0	30.1	48.1	0.00000	0
13b	380	1240	3.27	11.9	13.3	0.0	11.5	63.3	0.00000	0
14a	600	425	0.71	7.1	1.5	27.3	7.1	57.0	0.00000	0
14b	660	1300	1.97	7.9	6.1	5.9	11.0	69.1	0.00013	2
15a	600	750	1.25	7.5	3.8	10.2	17.0	61.5	0.00015	2
15b	600	1005	1.68	15.8	2.6	20.1	17.5	44.0	0.00010	2
16a	340	1350	3.97	4.7	15.7	0.6	6.3	72.7	0.00012	2
16b	315	1250	3.98	9.8	11.0	4.7	4.6	69.9	0.00013	2
17a	600	985	1.64	6.0	10.7	0.0	18.1	65.2	0.00000	0
17b	495	1260	2.55	3.7	14.5	1.4	8.4	72.0	0.00000	0
18a	600	490	0.82	7.7	4.4	0.0	30.1	57.8	0.00000	0
18b	600	890	1.49	15.7	2.7	0.0	24.5	57.1	0.00000	0
20a	600	1250	2.08	8.9	4.0	16.6	10.7	59.8	0.00005	1
20b	600	1280	2.13	7.5	6.8	9.6	9.6	66.5	0.00001	0
Average before cabbage.....			1.55	9.8	4.4	4.8	19.1	61.9	0.00019	3
Average after cabbage.....			2.34	10.5	6.8	3.5	13.9	64.3	0.00014	2

in 12 normal individuals the flatus excretion was first determined on an ordinary (cabbage free) diet. On the day following this determination 300 gm. of raw brussel sprouts were given at 9:30 a.m., and 300 gm. of boiled brussel

sprouts at 5:30 p.m. and the gas excretion measured in the usual two 5-hour periods (9 a.m. to 2 p.m. and 5 p.m. to 10 p.m.).

TABLE 5

*The quantity and composition of colonic flatus in 15 normal individuals on an ordinary diet before (a) and after (b) intake of 50 gm. of lactose*

EXPERIMENT NO.	MIN.	FLATUS	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
		ml.	ml./min.	%	%	%	%	%	%	mg./ cu. m.
21a	600	1350	2.26	0.7	9.5	0.6	2.1	87.2	0.00004	1
21b	600	710	1.18	10.3	3.6	0.0	16.1	70.0	0.00008	1
22a	600	100	0.17	2.5	20.0	5.0	5.0	67.5	0.00000	0
22b	600	250	0.42	7.9	1.6	0.0	17.9	72.6	0.00000	0
23a	570	650	1.14	21.8	0.7	16.6	1.7	59.2	0.00009	1
23b	600	900	1.50	19.0	1.6	7.9	0.0	71.5	0.00000	0
24a	600	625	1.04	14.7	0.5	21.4	17.7	45.7	0.00009	1
24b	600	300	0.50	9.4	2.7	17.0	9.6	61.3	0.00037	6
25a	570	2800	4.91	1.6	20.0	0.8	2.0	75.6	0.00004	1
25b	450	2800	6.23	3.2	15.1	0.8	2.8	77.1	0.00000	0
26a	600	275	0.46	7.1	5.5	1.2	6.9	79.3	0.00041	7
26b	600	150	0.25	9.7	0.0	10.0	17.0	63.3	0.00037	6
27a	600	1300	2.16	9.6	0.9	0.0	15.8	73.7	0.00004	1
27b	600	1100	1.84	16.9	0.0	0.0	39.5	43.6	0.00000	0
28a	600	400	0.67	18.5	3.7	0.0	25.0	52.8	0.00000	0
28b	600	1800	3.00	21.4	4.3	0.0	32.6	41.7	0.00000	0
29a	630	340	0.54	5.8	1.4	1.4	8.3	83.1	0.00049	8
29b	600	300	0.50	6.1	4.9	0.0	9.0	80.0	0.00037	6
30a	630	1400	2.22	4.5	9.4	0.0	1.2	84.9	0.00000	0
30b	630	1700	2.70	2.3	9.9	0.0	0.8	87.0	0.00007	1
31a	600	2800	4.67	2.1	17.8	0.8	0.4	78.9	0.00002	0
31b	600	850	1.42	1.1	19.0	0.0	1.3	78.6	0.00045	7
32a	600	550	0.92	7.5	1.7	4.7	10.4	75.7	0.00010	2
32b	600	800	1.33	5.8	2.8	8.4	13.2	69.8	0.00007	1
33a	600	900	1.50	16.8	9.3	4.1	3.8	66.0	0.00000	0
33b	600	730	1.22	13.6	9.4	0.0	9.4	67.6	0.00023	4
34a	600	1300	2.17	2.5	6.2	0.0	6.5	84.8	0.00009	1
34b	600	1350	2.25	1.8	4.5	1.2	9.5	83.0	0.00008	1
35a	600	550	0.42	3.7	6.7	0.0	5.5	84.1	0.00010	2
35b	600	625	1.04	10.3	11.1	0.0	2.8	75.8	0.00009	1
Average before lactose.....			1.71	8.0	7.6	3.8	7.5	73.1	0.00010	2
Average after lactose.....			1.70	9.3	6.0	3.0	12.2	69.5	0.00015	3

The results, which are presented in Table 4, show that the intake of cabbage results in a definite increase in the flatus production, the average value after the cabbage ingestion being 2.34 ml. per minute as compared to 1.55 ml. in the preceding control period. The analyses reveal that it is especially the



nitrogen content which is increased. This finding suggests that the increased flatus excretion is mainly caused by a livelier peristalsis, which results in the passage of larger amounts of atmospheric air through the intestine.

*c. The effect of intake of lactose and cow's milk*

In view of the interest evidenced in the dietetic literature on the digestion of lactose and cow's milk in the intestine, investigations on the effect of lactose

TABLE 6

*The quantity and composition of colonic flatus in 10 normal individuals on an ordinary diet before (a) and after (b) intake of 1 liter of cow's milk*

EXPERIMENT NO.	MIN.	FLATUS	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
		ml.	ml./min.	%	%	%	%	%	%	mg./cu. m.
36a	600	300	0.50	12.1	0.0	0.0	24.2	63.7	0.00000	0
36b	600	525	0.88	17.2	0.0	0.0	20.2	62.6	0.00011	2
37a	600	225	0.38	9.1	10.3	0.0	12.7	67.9	0.00025	4
37b	600	175	0.29	7.0	5.2	2.6	13.9	71.3	0.00064	11
38a	600	1100	1.84	15.4	4.3	7.3	36.5	36.5	0.00015	3
38b	600	725	1.21	6.2	3.9	10.4	36.3	43.2	0.00008	1
39a	600	825	1.37	8.1	3.7	0.0	3.1	85.1	0.00007	1
39b	600	1100	1.84	5.9	3.7	10.6	13.3	66.5	0.00010	2
40a	600	410	0.68	11.4	3.2	0.0	19.2	66.2	0.00000	0
40b	600	125	0.25	15.4	0.0	3.1	27.7	53.8	0.00000	0
41a	600	350	0.59	9.0	0.0	1.0	19.3	70.7	0.00016	3
41b	600	525	0.88	9.3	0.0	0.0	25.4	65.3	0.00021	3
42a	600	1050	1.75	12.9	0.0	0.0	37.2	49.9	0.00000	0
42b	600	735	1.23	12.1	0.4	9.5	33.6	44.4	0.00008	1
43a	600	750	1.25	13.4	0.0	0.0	5.1	81.5	0.00015	3
43b	600	500	0.84	10.0	0.7	0.0	10.7	78.6	0.00022	4
44a	600	850	1.42	24.7	1.4	11.0	35.2	24.7	0.00013	2
44b	600	500	0.84	12.5	0.0	34.1	0.0	53.4	0.00011	2
45a	600	450	0.75	5.4	2.0	1.3	3.6	87.7	0.00000	0
45b	600	500	0.84	9.1	0.0	0.0	6.6	84.3	0.00011	2
Average before milk.....			1.05	12.2	2.5	2.1	19.6	63.6	0.00009	2
Average after milk.....			0.90	10.5	1.4	7.0	18.8	62.3	0.00017	3

and milk ingestion on the volume and composition of excreted flatus were carried out in 15 and 10 normal individuals respectively<sup>13</sup>. The subjects had received a cabbage and milk free diet for several days before the test and during the control experiment. On the day of experiment 50 gm. of lactose or 1 liter of cow's milk was given at 9:30 a.m.

As will be seen from Tables 5 and 6 the intake of lactose and milk caused no significant change in the amount or composition of excreted flatus.

THE QUANTITY AND COMPOSITION OF COLONIC FLATUS IN PATIENTS WITH THE COLITIS SYNDROME

a. *Values observed on an ordinary, cabbage free and milk free diet*

As meteorism and flatulence are prominent symptoms in patients suffering from the colitis syndrome the results of quantitative flatus analyses in this

TABLE 7

*The quantity and composition of colonic flatus in 22 patients with the colitis syndrome on an ordinary, cabbage-free and milk-free diet*

	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
	ml./min.	%	%	%	%	%	%	mg./cu. m.
Average.....	0.95	8.9	4.2	3.9	7.2	76.0	0.00010	2

TABLE 8

*The quantity and composition of colonic flatus in 7 patients with the colitis syndrome before (a) and after (b) intake of 50 gm. of lactose*

EXPERIMENT NO.	MIN.	FLATUS	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
		ml.	ml./min.	%	%	%	%	%	%	mg./cu. m.
46a	600	230	0.38	12.9	0.0	14.7	0.0	72.4	0.00000	0
46b	600	550	0.92	10.8	0.0	0.0	7.6	81.6	0.00010	2
47a	600	600	1.00	15.7	1.7	0.0	2.8	79.8	0.00000	0
47b	600	300	0.50	13.3	1.7	0.0	1.3	83.7	0.00000	0
48a	600	350	0.58	13.4	0.0	0.0	37.6	49.0	0.00015	3
48b	600	600	1.00	10.9	0.0	0.0	31.2	57.9	0.00000	0
49a	600	780	1.30	23.6	0.3	0.0	1.9	74.2	0.00000	0
49b	600	700	1.06	16.4	0.5	0.0	0.0	83.1	0.00000	0
50a	600	250	0.42	4.7	0.0	0.0	4.2	91.1	0.00000	0
50b	600	200	0.33	6.4	0.0	0.7	0.0	92.9	0.00000	0
51a	600	600	1.00	0.0	12.9	5.6	0.0	81.5	0.00000	0
51b	600	380	0.63	9.4	0.6	0.0	9.4	80.6	0.00000	0
52a	600	300	0.50	7.9	4.6	1.7	0.3	85.0	0.00000	0
52b	600	460	0.77	8.7	5.5	0.0	14.7	70.9	0.00000	0
Average before lactose.....				0.74	11.2	2.8	3.1	75.8	0.00002	0
Average after lactose.....				0.75	10.8	1.4	0.1	78.5	0.00001	0

condition was anticipated with special interest. A total of 22 patients, who gave the usual complaints of intestinal spasms and abdominal fullness, but in whom no ulcerative lesions or major pathological changes were evidenced by proctoscopic examination, were subjected to the study. During the period of observation the patients received an ordinary diet with the omission of cabbage and milk.

The results of the findings in 20 of the 22 patients may be derived from Tables 8 and 9, whereas the summarized results for the 22 subjects are given below in Table 7.

The analyses show an average excretion of only 0.95 ml. flatus per minute. This observation permits the important conclusion that the amount of flatus

TABLE 9

*The quantity and composition of colonic flatus in 13 patients with the colitis syndrome before (a) and after (b) intake of 1 liter of cow's milk*

EXPERIMENT NO.	MIN.	FLATUS	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
		ml.	ml./min.	%	%	%	%	%	%	mg./cu. m.
53a	600	900	1.50	11.2	6.4	5.1	10.4	66.9	0.00000	0
53b	600	2800	4.67	9.2	8.2	6.7	7.7	68.2	0.00000	0
54a	600	325	0.54	5.4	8.0	0.0	4.9	81.7	0.00016	3
54b	600	325	0.54	9.4	9.3	0.0	9.7	71.6	0.00032	5
55a	600	375	0.63	13.0	5.4	17.4	2.1	62.1	0.00028	5
55b	600	525	0.88	11.9	5.3	13.2	4.1	65.5	0.00000	0
56a	600	350	0.58	3.7	9.1	4.2	13.2	69.8	0.00036	6
56b	600	350	0.58	5.0	8.2	0.0	17.9	78.9	0.00029	5
57a	600	350	0.58	10.3	2.7	7.6	11.1	68.3	0.00015	3
57b	600	700	1.17	7.5	6.3	7.2	11.7	77.3	0.00017	3
58a	600	100	0.16	12.9	10.9	0.0	7.0	69.2	0.00000	0
58b	600	110	0.18	9.9	12.8	4.3	14.1	58.9	0.00000	0
59a	600	820	1.37	8.4	0.0	7.9	0.0	83.7	0.00026	4
59b	600	500	0.83	9.3	0.0	7.9	10.4	72.4	0.00021	3
60a	600	750	1.25	10.6	0.0	0.0	8.1	81.3	0.00017	3
60b	600	830	1.38	6.0	9.0	0.0	6.1	78.9	0.00000	0
61a	600	2700	4.50	1.3	5.9	5.2	0.0	87.6	0.00000	0
61b	600	320	0.53	7.7	6.5	6.5	8.8	70.5	0.00009	1
62a	600	200	0.33	7.1	2.1	0.0	15.7	75.1	0.00017	3
62b	600	380	0.63	6.9	3.5	0.0	19.7	69.9	0.00000	0
63a	600	900	1.50	8.0	2.4	0.0	15.1	74.5	0.00000	0
63b	600	850	1.42	7.6	4.6	2.0	7.5	78.3	0.00009	1
64a	600	210	0.35	5.3	6.0	0.0	0.0	88.7		
64b	600	120	0.20	6.7	1.7	0.0	3.3	88.3		
65a	600	550	0.92	5.7	2.7	4.9	5.7	81.0	0.00000	0
65b	600	310	0.52	4.2	6.3	2.0	6.1	81.4	0.00000	0
Average before milk.....			1.09	7.9	4.7	4.0	7.2	76.2	0.00013	2
Average after milk.....			1.08	7.8	6.3	3.8	9.8	72.3	0.00010	2

excreted by patients with the colitis syndrome is not greater than found under normal conditions and supports the view that the complaints of these patients are caused by an increased state of irritability of the intestinal wall with a resulting greater tendency for the development of colonic spasms rather than by an increased formation of intestinal gas. This contention thus places the site of the disease in the intestine itself rather than in its gaseous contents.

b. *The effect of intake of lactose and cow's milk*

It is a well known experience from the daily medical practice that a large percentage of patients suffering from the colitis syndrome claim to tolerate milk and milk dishes poorly, the intake of such food usually being followed by an aggravation of the complaints. In view of the actuality of this problem and the absence of objective data an investigation of the intake of milk on the volume of excreted flatus was considered to be of great importance. For this reason the effect on the flatus excretion of ingestion of 50 gm. of lactose and 1 liter of cow's milk was studied in respectively 7 and 13 patients with the colitis

TABLE 10

*The quantity and composition of colonic flatus in 10 patients with cardiac decompensation*

EXPERIMENT NO.	MIN.	FLATUS	FLATUS	CO <sub>2</sub>	O <sub>2</sub>	CH <sub>4</sub>	H <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> S	H <sub>2</sub> S
		ml.	ml./min.	%	%	%	%	%	%	mg./cu. m.
66	300	150	0.50	13.3	6.7	0.0	10.0	70.0	0.00034	6
67	300	400	1.33	11.8	0.9	0.0	8.5	78.8	0.00013	2
68	300	500	1.67	2.5	11.4	8.4	0.0	77.7	0.00000	0
69	600	750	1.25	8.8	5.2	0.0	3.6	82.4	0.00014	2
70	600	600	1.00	6.5	7.8	3.3	12.4	70.0	0.00009	1
71	300	160	0.53	5.0	7.0	5.0	8.8	75.0	0.00000	0
72	300	175	0.58	13.9	0.0	23.5	15.7	46.9	0.00034	6
73	600	470	0.77	8.7	3.3	1.7	0.0	86.3	0.00000	0
74	300	100	0.33	2.1	11.3	4.2	3.1	79.3	0.00017	3
75	300	210	0.70	6.3	8.0	1.2	0.0	84.5	0.00000	0
Average.....			0.87	7.9	5.2	4.7	6.1	76.1	0.00012	2

syndrome, the experimental procedure being the same as that employed in the study of normal individuals described above. The results are presented in Tables 8 and 9, and as was the case in the normal individuals, fail to show any effect of the lactose and milk intake on the flatus volume and composition.

#### THE QUANTITY AND COMPOSITION OF COLONIC FLATUS IN PATIENTS WITH CARDIAC DECOMPENSATION

A perusal of the literature concerning the importance of circulatory decompensation for the development of meteorism does not result in any consistent opinion on this subject, the points of view of leading clinicians being widely divided. For the purpose of contributing to this problem a study was made on the flatus excretion of 10 patients with marked cardiac failure. The experimental period employed was 5-10 hours. The results, reproduced in Table 10 do not show any excessive flatus excretion under the condition of cardiac failure, the values on the contrary generally being lower than normal.

The low values found may possibly be explained by the reduced food and fluid intake of the patients.

#### SUMMARY

A report is given of a procedure for quantitative collection and analysis of human colonic flatus and results obtained by such studies presented.

The excretion of colonic gas was found to vary considerably between different individuals; the average value observed in 45 normal subjects was 1.47 ml. per minute. Carbon dioxide, hydrogen and nitrogen were constant constituents of the colonic flatus. Oxygen was present in most of the samples, whereas methane and hydrogen sulphide were occasionally lacking. The concentration of hydrogen sulphide when present was only small, valuing 0.0001 to 0.001 per cent.

Ingestion of brussel sprouts by normal individuals was followed by a marked increase in the volume of excreted flatus, whereas lactose and cow's milk were without effect on the quantity and composition of the flatus.

In patients suffering from the colitis syndrome no excess gas excretion could be demonstrated. Intake of lactose and cow's milk was likewise without effect on the amount and composition of the flatus in these subjects.

The volume of gas excreted by patients with cardiac decompensation was not increased.

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## DIGESTION AND ABSORPTION AFTER MASSIVE RESECTION OF THE SMALL INTESTINE\*

### I. UTILIZATION OF FOOD FROM A "NATURAL" VERSUS A "SYNTHETIC" DIET AND A COMPARISON OF INTESTINAL ABSORPTION TESTS WITH NUTRITIONAL BALANCE STUDIES IN A PATIENT WITH ONLY 45 CM. OF SMALL INTESTINE

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#### INTRODUCTION

Many cases have been reported in the medical literature<sup>1</sup> of patients who survived the loss of a greater part of their small intestine, but only in a few of these cases was intestinal absorption studied. Massive resection of the small intestine is necessitated most often by mesenteric thrombosis and occasionally by regional enteritis or abdominal wounds. In reviewing the cases in the literature from the standpoint of compatibility of extensive resection of the small intestine with life and health, Wildegans<sup>2</sup> came to the conclusion that loss of one-third of the intestine in man is consistent with maintenance of normal weight and strength. When between one-third and three-fourths of the small intestine is resected loss of weight and strength together with frequent attacks of diarrhea are the rule. Loss of over three-fourths of the intestine is followed by severe marasmus. Kunz and Molitor<sup>3</sup> confirmed these conclusions experimentally by showing that dogs are able to survive removal of 80 per cent of their small intestine provided that they received an optimum diet. The nutritional balance studies which were carried out in human beings surviving massive resection of the small intestine are in good agreement that the absorption of fats is impaired severely, the absorption of proteins is decreased moderately and the utilization of carbohydrates remains normal.

The present study of digestion and absorption in a patient with a short remnant of the small intestine was undertaken with two main objectives. The first was to compare by means of nutritional balance studies the degree of utilization of the various elements of a diet consisting of natural foods with the extent of utilization of the corresponding components of a "synthetic" diet. The second was to learn to what extent tests for intestinal absorption of the elementary foodstuffs help to determine the actual ability of the intestine to utilize these foodstuffs as shown by nutritional balance studies.

Our patient is a woman aged 47 who, in January, 1947, had a massive re-

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section of 435 cm. of the small intestine consisting of the entire ileum and all but the upper 15 cm. of the jejunum. The remainder of the jejunum was anastomosed to the mid-transverse colon. The resection was carried out because of mesenteric thrombosis following appendectomy.

The greatest problem in our patient has been the utilization of an adequate amount of food to maintain weight and strength. The patient's weight through adult life was about 64 kgm. As a result of the operation, the patient's weight decreased to a minimum of 39.4 kg. ten months after the operation. Thereafter, it increased to 42 kg. and has remained at this figure.

On good days the patient is able to ingest 2125 calories (P-150, F-65, CHO-200) of a bland diet but usually takes considerably less. This diet is supplemented by vitamins A (15,000 I. V.), D (3,000 units), B complex\* and C (300 mg.). The patient also receives regularly 12 gm. of calcium gluconate a day in addition to a quart of milk, and intermittently 0.6 gm. of ferrous sulfate. On such a regime she developed no clinical signs of hypocalcemia or any vitamin deficiency.

Her chief complaints are weakness; dizziness associated with vascular hypotension (B.P. is between 70/50 and 80/60); diffuse abdominal pains and nausea associated with visible bloating; and uncomfortable peristaltic movements. The patient has from three to six bowel movements a day. The stools are usually bulky, soft, foamy and have the color of putty, with a minimal odor. Occasionally they become liquid, brown in color, and acquire a foul odor. Undigested muscle fibers and starch particles occur in the stools in moderate numbers.

## METHODS AND RESULTS

### *Nutritional Balance Studies*

A diet containing 1610 calories (P-90, F-50, CHO-200) was chosen for these studies. A general diet consisting of "natural" foods calculated<sup>4</sup> according to these figures was offered to the patient and any items returned on the tray were subtracted. On the third day of the study a duplicate of each of the three meals as actually eaten by the patient was prepared, and analyzed for its content of protein, fat, and carbohydrate.

For comparison with this "natural" diet the patient subsequently received a "synthetic" formula of the following content: Protein hydrolysate†—75 gm., 20 per cent cream —180 cc.; and glucose —176 gm. These ingredients were mixed in 240 cc. of whole milk and flavored with 15 gm. of cocoa. This mixture possesses the same calculated food value as the "natural" diet. A portion

\* Thiamine—11 mg.; riboflavin—11 mg.; niacin—90 mg.; pyridoxine—3 mg.; and calcium pantothenate—21 mg.

† "Essenaminate" of Frederick Stearns Company.

of it was also subjected to chemical analysis. The patient was kept on each diet for six days.

Collection of feces and of urine in both balance studies was started 48 hours after the beginning of the experimental diets to allow time for the excreta reflecting the previous dietary regime to be eliminated. The nitrogen content of the meals, feces, and urine was determined by the method of Koch and McMeekin<sup>5</sup>. The fat content of the meals and feces was determined according to Saxon<sup>6</sup>. The carbohydrate contained in the meals and feces was determined by the procedure described by Hanes<sup>7</sup>.

TABLE I  
*Food intake—four day periods*

DIET	INTAKE	PROT.	FAT	CARB.	Ca	P	CALORIES	FLUIDS
		gms.	gms.	gms.	gms.	gms.		cc.
"Natural"	Calculated	260	194	693	9.01	5.46	5557	—
	Corrected	257	194	652	10.25	5.32	5382	10,395
"Synthetic"	Calculated	360	193	801	7.67	1.87	6377	—
	Corrected	338	183	773	8.13	2.16	6094	10,450

TABLE II  
*Fecal and urinary excretion—four day periods*

DIET	EXCRETA	N <sub>2</sub>	FAT	CARB.	Ca	P
		gms.	gms.	gms.	gms.	gms.
"Natural"	Urine*	24.72	—	—	0.98	0.79
	Feces	15.47	149	9	12.27	3.98
"Synthetic"	Urine†	26.72	—	—	0.89	0.0
	Feces	25.56	131	9	10.81	2.56

\* Total output 4,700 cc.

† Total output 4,175 cc.

While on the diet of natural foods the patient ate to the limit of her ability but did not quite reach her goal. A constant complaint was gaseous distention which was verified objectively. After beginning the "synthetic" diet the patient rapidly lost her flatulence. During each study the patient lost 0.3 kg. in weight.

Data pertaining to the food intake during the two balance studies are given in Table I. Data for the excretion of various substances in the urine and feces are reported in Table II. In Fig. 1 the total food intake and food utilization on the two diets are shown graphically. During both studies the patient was in a slightly positive nitrogen balance retaining respectively 0.22 gm. and 0.47 gm. of nitrogen per day.



### Calcium and Phosphorus Balance Studies

During both dietary periods the patient was on a moderately negative calcium balance in spite of a fairly large calcium intake (Tables I and II). The negative calcium balance was somewhat more pronounced on the lower calcium intake during the "synthetic" diet. The phosphorus balance was slightly positive on the "natural" diet and became slightly negative on the much lower phosphorus intake of the "synthetic" diet (Tables I and II). The patient's serum calcium was 9.5 mg. per cent and the serum phosphorus was 4.1 mg. per cent. At no time since her operation did the patient have any clinical manifestations of tetany. Basic serum phosphatase was estimated at 6 Bodansky

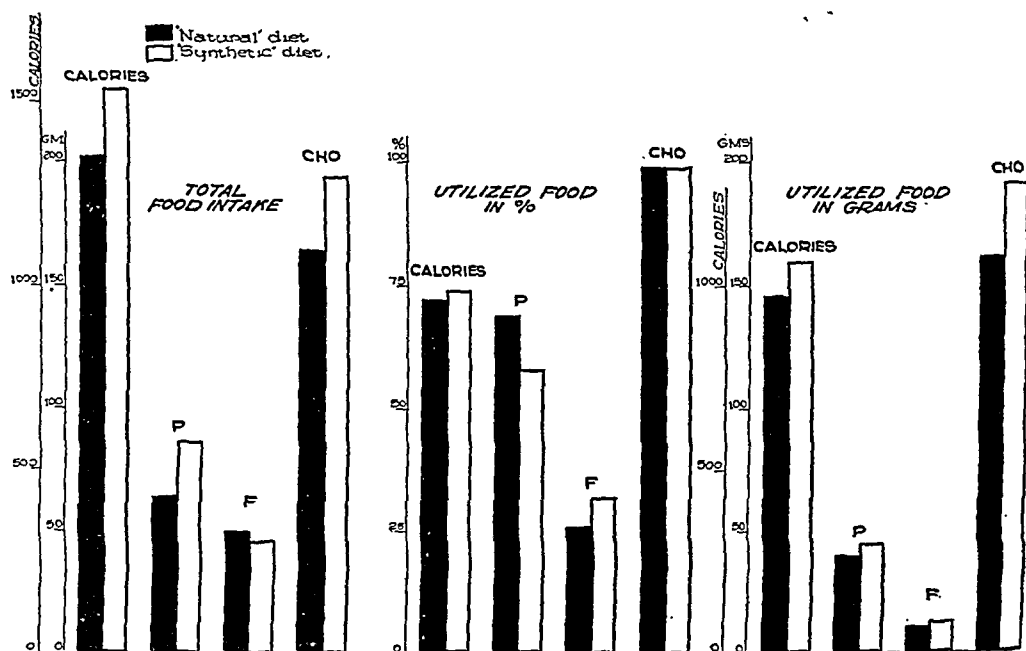


FIG. 1. COMPARATIVE NUTRITIONAL BALANCE STUDY OF PATIENT WITH 18 INCHES OF SMALL INTESTINE

units and acid serum phosphatase was found to be 1 Bodansky unit. Radiologically there was no evidence of an appreciable loss of calcium from the bones.

### Tests of Intestinal Absorption

In order to obtain in our patient a separate estimation of the rate of intestinal absorption for each of the three fundamental food elements, the following procedures were used.

1) *Oral Methionine Tolerance.* As a test for absorption of amino-acids an oral methionine tolerance curve was used as described by Harper and Uye-

yama<sup>8</sup> from our clinic. In this procedure 1 gm. of DL methionine for every 15 kgm. of weight is given by mouth and the curve of the L isomere in the plasma is determined at intervals for four hours by a micro-biological method. The fasting plasma level of methionine in our patient was normal. The rest of the curve was considerably below the lowest figures obtained in four controls (Fig. 2).\*

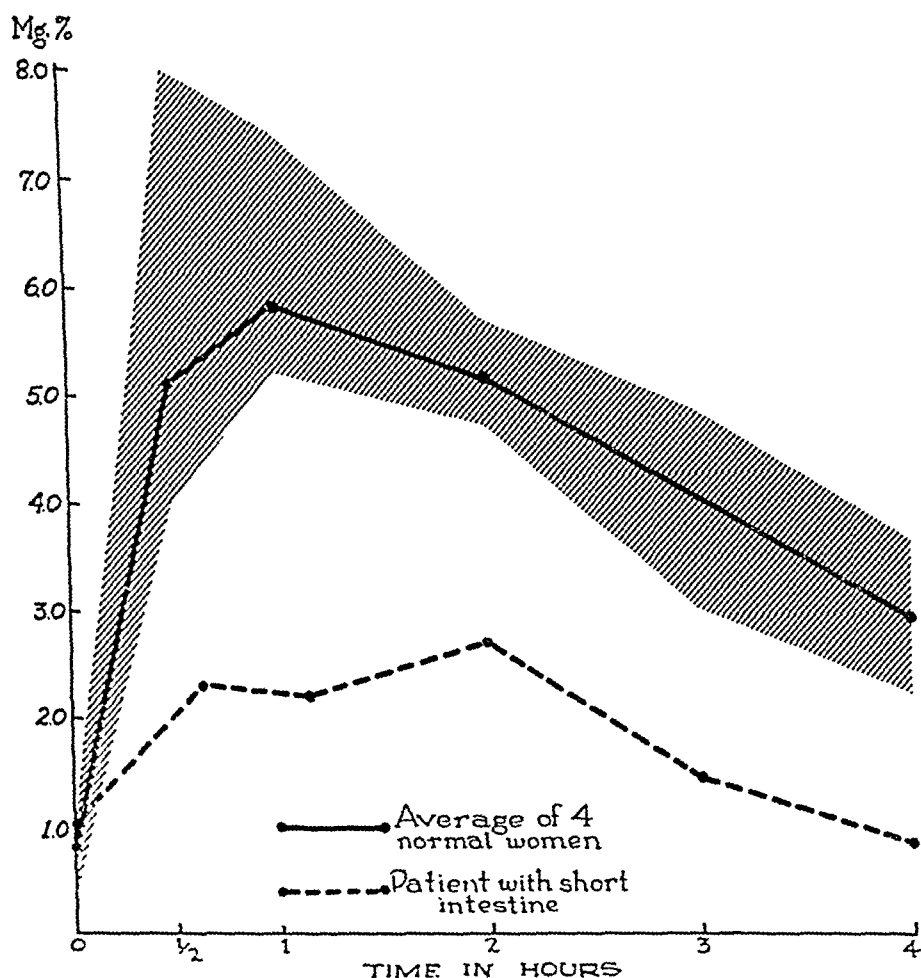


FIG. 2. ORAL METHIONINE TOLERANCE CURVES

The mean value of the curve was only about 40 per cent of the average of the controls. In addition the peak of the curve was reached in two hours instead of in one hour as in the average curve.

2) *Oral Vitamin A Tolerance.* As a test for absorption of fats the vitamin A content of the plasma four hours after oral administration of 7,000 I. U. of this vitamin per kilogram of body weight was used according to Chesney and

\* Shaded area shows the highest and lowest values obtained in our controls.

McCoord<sup>9</sup> but vitamin A determinations were carried out by the method of Kaser and Stekol<sup>10</sup>. The basis of this test are the observations that vitamin A is carried across the intestinal mucosa by lipids and that its absorption was found to parallel the absorption of fats. The fasting level of vitamin A in the plasma of our patient was lower than that in any of ten control patients. It amounted to 34 per cent of the average of these patients. The plasma level

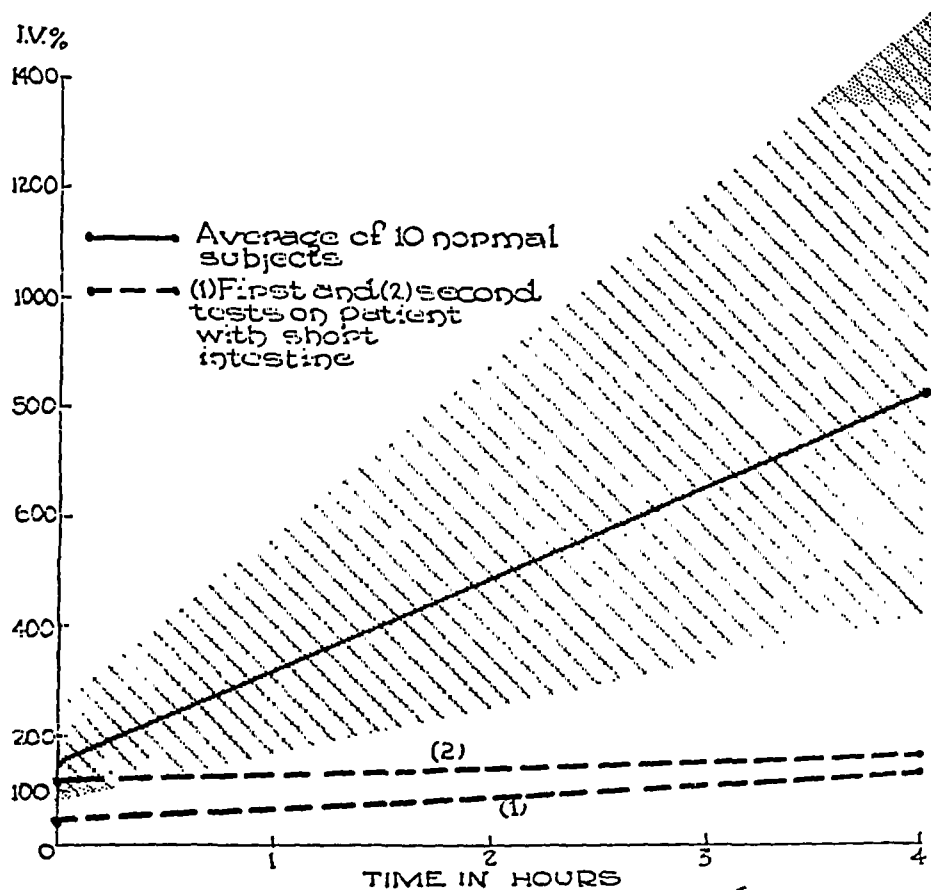


FIG. 3. ORAL VITAMIN A TOLERANCE TEST

of vitamin A four hours after ingestion of the test dose was also very low (Fig. 3)\*. A second test performed five days later in order to determine whether chronic depletion of vitamin A in the liver was a factor in the low plasma value at the end of the first test showed a low normal fasting level. Four hours after the second test dose the level of vitamin A in the plasma amounted only to 8 per cent of the average normal increase at this period.

There were between 12.8 and 14.9 micrograms per cent of carotene in the

\* Shaded areas shows the highest and lowest values obtained in our controls.

serum of our patient corresponding to the four determinations of vitamin A. The normal values are considered to be above 100 micrograms per cent<sup>11</sup>.

3) *Oral Galactose Test.* As one test for absorption of sugars the galactose tolerance curve after oral administration of 40 gm. of galactose as described by one of us (T.L.A.<sup>12</sup>) was performed twice. On the first occasion no galactose could be detected in any of the specimens of blood. On the second occasion 9 mg. per cent of galactose was found in a single specimen of blood obtained half an hour after administration of galactose. Normally the average peak of the oral galactose tolerance curve reaches 20 mg. per cent.

4) *Oral and Intravenous Glucose Tolerance Tests.* To test the absorption of glucose a conventional glucose tolerance test after oral administration of 100 gm. of glucose was also carried out. At the one hour period the curve rose to a peak only 25 mg. per cent above the fasting level and took three hours to return to its original level. According to Todd and Sanford<sup>13</sup> normally a maximum rise of about 60 mg. per cent which returns to the fasting level in two hours is expected in this test. As a check on possible depletion of carbohydrate in the body with consequent abnormally rapid utilization of sugar the intravenous glucose tolerance test with 25 gm. of this sugar was performed with normal results.<sup>14</sup>

#### *Other pertinent laboratory data*

*Protein Metabolism*—Total serum proteins at the time of this study were 4.62 gm., with 2.40 gm. of albumin and 2.22 gm. of globulin. The nonprotein nitrogen was 29 mg. per cent. The prothrombin level fluctuated spontaneously between 48 and 74 per cent.

*Fat Metabolism*—The total blood cholesterol was 167 mg. per cent.

*Vitamin Levels in the Blood*—a) The thiamine chloride level was 12.9 micrograms per cent. Anything above 5.0 micrograms per cent is usually considered normal. b) No ascorbic acid could be detected by the method of Farmer and Abt<sup>15</sup> in the plasma of our patient on two successive days. After the patient was given 200 mg. of ascorbic acid a day orally\* for four days there still was no ascorbic acid in the plasma. After receiving the same dose of ascorbic acid for 24 days her fasting plasma level finally rose to 0.11 mg. per cent. At no time did the patient exhibit any clinical signs of ascorbic acid deficiency.

*Electrolyte Balance*—The serum sodium was 137.5 mEq/l and the serum potassium was 3.4 mEq/l indicating slightly depressed levels of these electrolytes without any clinical manifestations.

*Gastric Analysis*—The fasting specimen contained 60° of free acid and 16° of combined hydrochloric acid. Specimens following the alcohol meal con-

\* Administration of ascorbic acid was temporarily discontinued after entry to the hospital.

tained no free acid but did contain between 6° and 10° of combined hydrochloric acid. Pepsin and rennin were absent. None of the specimens were stained by bile.

*Liver Function Tests*—a) In the intravenous hippuric acid test 0.61 gm. of this acid was excreted in 157 cc. of urine during one hour. This indicates slight impairment of function since the normal figures are 0.7 to 1.0 gm. b) The thymol turbidity test showed 4 units. The normal limits for this test are 1 to 5 units.

#### DISCUSSION

On a diet of natural foods our patient utilized 62 per cent of ingested protein which compares favorably with the 76 per cent utilization of protein described by West, Montague and Judy<sup>16</sup> and by Todd, Dittebrandt, Montague and West<sup>17</sup>, in a patient who had 90 cm. of the small intestine left as against the 45 cm. remaining in our patient. The proportion of protein actually used by both patients was somewhat greater since it is known that a person in nitrogen equilibrium excretes about 10 per cent of the "waste" nitrogen in the feces. When this nitrogen is subtracted from the total nitrogen of the feces in calculating the food protein actually lost, it is seen that our patient utilized 69 per cent of her dietary protein.

On the "synthetic" diet our patient utilized 53 per cent of the ingested protein which was in the form of a protein hydrolysate. After correction for the "waste" fecal nitrogen this figure is increased to 58 per cent. Thus we see that there was a somewhat greater utilization of the natural protein than of hydrolysate amounting to 19 per cent. There are two possible explanations for this unexpected finding. The first is that the patient was able to eat less than the planned amount of the "natural" diet. In favor of this explanation is that if one considers the total amount of protein used per day one will see that on the "synthetic" diet she actually utilized 13 per cent more protein than on the "natural" diet. In other words, the less complete utilization of the protein hydrolysate suggests that on the "synthetic" diet the patient may have reached her limit of protein absorption. The second explanation is that as claimed by Free and Leonards<sup>18</sup>, the gastro intestinal tract may actually handle unhydrolyzed protein more readily than an equivalent amount of amino acids. An important factor in this seeming paradox may be the high osmotic pressure of protein hydrolysates.

It was noted that at the time of our studies the patient was in a slightly positive nitrogen balance, but that in spite of this, she had a low serum albumen. This discrepancy is probably explained by the fact that our studies were carried out during one of the patient's "good" periods which alternate with spells of diarrhea, nausea and some vomiting. It is during these "bad"

periods that a negative nitrogen balance can be expected to lead to a gradual lowering of the serum albumen. This reasoning is supported by the absence of significant hepatic insufficiency as shown by liver function tests.

On the diet of natural foods our patient was able to use only 23 per cent of the ingested fat as against a 55 per cent utilization of fat by the patient of West et al. This difference assumes even greater significance when one takes into consideration that the latter patient consumed from three to four times as much fat as our patient utilizing daily up to 93 grams of fat as against 11 grams in the case of our patient. It confirms the much greater importance of the presence of a fair length of small intestine for the absorption of fat than for the absorption of protein or carbohydrate. In attempting to arrive at a figure more nearly representing the true extent to which fat is absorbed certain corrections were tentatively considered. According to one view fecal fat in normal individuals represents chiefly the unabsorbed residue of fat in the diet and according to the recent work of Wollaeger, Comfort and Osterberg<sup>19</sup> who also cite the work of others, amounts to between 4 and 10 per cent of ingested fat depending on the proportion of saturated fatty acids of eighteen or more carbon atoms which it contains. According to another view in favor of which Annegers, Boutwell and Ivy<sup>20</sup> recently brought out new evidence, fecal fat excretion in normal individuals is independent of the dietary fat intake and amounts to  $4 \pm 1$  gm. a day. In either case the correction allowable for the utilization of fat in our patient is insignificant raising it only to about 25 per cent.

On the "synthetic" diet, our patient utilized 29 per cent of the ingested fat. The total daily utilization of fat on this diet was 18 per cent greater than on the "natural" diet. The slightly better utilization of fat on the "synthetic" diet may be due to a greater digestibility of cream as compared to mixed fats.

The fasting level of vitamin A in the plasma of our patient was low as compared to our controls, but would be considered normal according to some of the data in the literature. There are considerable regional variations in the "normal" plasma level of vitamin A and we have no wish to stress this factor here. On the other hand, the low level of vitamin A in the plasma of our patient following the oral vitamin A tolerance test (8 per cent of the average for our controls) more fully indicates a marked impairment of absorption. The end test level of the serum in our patient was also very low.

The low plasma vitamin level found at times indicates severely restricted absorption of vitamin A, since no significant hepatic insufficiency was observed in liver function tests.

The total fat intake was about 100 gm. resulting in partially complete utilization of about 25 per cent of the "natural" or "synthetic" diets and are in accord with the average of 10 per cent reported by The Enders that our patient utilized

19 per cent more carbohydrate per day on the "synthetic" diet is due entirely to the greater intake during this period. However, these findings are at variance with the results of both oral sugar tolerance tests and with certain clinical observations. The galactose as well as the glucose blood sugar curves after oral administration of these sugars were abnormally low and in addition, the latter curve was also unusually protracted. Since the intravenous glucose tolerance test did not indicate abnormally rapid disappearance of this sugar from the blood stream, we are justified in interpreting these results as indicating decreased intestinal absorption of sugars. This was even more so in relation to starches as shown by our observation that the pronounced abdominal distention in our patient while on the "natural" diet disappeared when she was put on the "synthetic" diet in which glucose was the only source of carbohydrate. It is of interest that West et al.<sup>16</sup> and other authors also stressed the distended and tympanitic abdomen of patients after massive resection of the small intestine. Data obtained in man by the use of the Miller-Abbott tube show that solutions of glucose are absorbed to a large extent in the duodenum and upper jejunum. On the other hand starch which must undergo enzymatic hydrolysis before absorption is presumably absorbed lower in the small intestine. For this reason one would expect that a much larger proportion of starch than of glucose would reach the colon of patients with a short intestine to undergo bacterial fermentation with production of gas. To pursue this possibility further we tested the combined effects of oral administration of sulfathalidine and penicillin on the bloating of our patient. We found that the partial sterilization of the colon achieved in this manner resulted in a definite reduction of bloating.

These considerations and the fact that after bacterial fermentation sugars and starches elude the chemical methods employed for quantitative determinations of carbohydrates in the feces make us discount the apparently normal utilization of carbohydrates in our patient and other patients when it is based on the finding of only minimal amounts of carbohydrate in the feces. We believe that the sugar tolerance tests which indicate an important impairment of intestinal absorption in our patient are more reliable. It is also permissible to assume that the absorption of starches is diminished even more than that of sugars in our patient and in other patients with severe impairment of the function of the small intestine from any cause.

The corrected figures for overall utilization of calories in our patient are 72 per cent of normal on a "natural" diet versus 76 per cent of normal on a "synthetic" diet. On the "synthetic" diet the patient was able to consume and to use about 15 per cent more calories due chiefly to absence of digestive discomfort. However, the patient refused to continue the "synthetic" diet for any length of time even with supplemental feedings of natural foods.

Over the short period of the two nutritional balance studies there was no difference in the behaviour of the patient's weight.

From a comparison between the discussed balance studies two conclusions can be drawn. The first is that the human small intestine is far more important for the absorption than for the digestion of food. The second is that the clinical advantages of predigested or "synthetic" foodstuffs in diseases of the small intestine are of limited scope especially if these foodstuffs begin to clash with the tastes of the patient.

In comparing the results of our nutritional balance studies with those of the absorption tests for single food elements it is apparent that the impairment of intestinal absorption of proteins and fats is greater when judged by the absorption tests than by the outcome of the balance studies. This difference is due to two reasons: In performing the absorption tests the full load of each test was imposed on our patient whereas in the balance studies the intake of food was considerably below normal. In absorption tests the time element is strictly taken into consideration whereas in balance studies there is opportunity for compensation through overtime work on the part of the disabled intestine since the absorptive capacity of the normal intestine is not taxed to the limit in such studies. In application to the absorption of carbohydrates the results of balance studies are completely unreliable for the already mentioned reasons. In application to the absorption of proteins and fats both methods of estimating intestinal absorption are valuable and complement each other. The conclusion also appears justified that tests of intestinal absorption while still in an early stage of development are less time consuming and less expensive than dietary balance studies and promise to be more practical for clinical purposes.

Regarding the calcium balance in our patient it is of interest that in spite of a negative balance during the period of study, she never exhibited any signs of calcium deficiency. This was confirmed by normal serum calcium values. By contrast many patients surviving massive resection of the small intestine were reported to suffer from hypocalcemic tetany even though they retained a longer remnant of the jejunum than our patient. The explanation of this difference almost certainly lies in the fat content of the diet since calcium is known to be carried out in the feces as calcium soaps of unabsorbed fatty acids. In this respect we are particularly interested in the patient reported by West et al.<sup>16</sup> who had 90 cms. of small intestine left and suffered from repeated severe attacks of tetany with a low serum calcium level. These authors state that their patient insisted on eating large amounts of fat and had a fairly constant ratio of fecal calcium to fecal fat between 0.023 and 0.030. In our patient this ratio was 0.021 although her fat intake was only from one-fourth to one-third that of the other patient. The relative constancy of this



ratio in different patients at different levels of fat intake lends support to the above mentioned mechanism by which patients with excessive amounts of fatty acids in the stools are deprived of their ingested calcium.

In spite of absence of clinical signs of an ascorbic acid deficiency our patient had extremely low ascorbic acid levels in the plasma. These low levels were affected very little by oral administration of ascorbic acid over a period of weeks amounting to three times the average daily requirement in addition to the supply furnished by the diet. This observation seems to indicate that ascorbic acid needs for its absorption a considerable length of small intestine and appears to contradict the finding of Nicholson and Chornock<sup>21</sup> obtained through intubation experiments that ascorbic acid in pure solution is avidly absorbed in small segments of the duodenum and jejunum. Perhaps the explanation of this discrepancy lies in the fact that under ordinary conditions ascorbic acid competes for intestinal absorption with a great many other food elements which retard its absorption. By contrast with ascorbic acid the blood level of thiamine chloride in our patient was normal.

#### SUMMARY AND CONCLUSIONS

1. The case is reported of a patient who survived the resection of 90 per cent of the small intestine and after ten months reached a nutritional equilibrium, making a good subject for the study of problems bearing on the diagnosis and treatment of diseases of the small intestine.

2. No striking differences were found in the degree of utilization of a diet consisting of natural foods as compared to a "synthetic" diet. On the "natural" diet proteins and on the "synthetic" diet, fats were utilized somewhat better. The patient was more comfortable on the "synthetic" diet and was able to take somewhat larger amounts of it, but after a few weeks refused to take considerable amounts of the "synthetic" formula even in combination with natural foods. These results show that the small intestine is much more important for the absorption than for the digestion of food, and that predigested foods have only a limited use in diseases of the small intestine except for intravenous administration during acute phases.

3. Impairment of intestinal absorption of proteins and of fats as judged by absorption tests was greater than that demonstrated in the same patient by nutritional balance studies. One reason for this is that the full load of each absorption test was imposed on our patient whereas the intake of food in the balance studies was below normal. Another reason is that in absorption tests the element of time is strictly controlled while in balance studies there is an opportunity for overtime work by the disabled intestine. The greatest divergence between absorption tests and balance studies was found in regard to carbohydrates, because destruction of the latter by bacterial action in the colon

renders nutritional balance studies entirely unreliable where carbohydrates are concerned.

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## A HISTO-PHYSIOLOGICAL STUDY OF THE EFFECT OF INTRAARTERIAL INJECTION OF ACETYLCHOLINE UPON THE GASTRIC MUCOSA OF THE DOG

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### INTRODUCTION

The effect of comparatively stable choline esters, such as mecholyl, upon gastric secretion has been studied extensively<sup>1-7</sup>. As recognized by Gray and Ivy<sup>5</sup>, when mecholyl is injected subcutaneously into total gastric pouch dogs it may, depending on the dose, stimulate a secretion of hydrochloric acid or cause an inhibition of acid secretion. These findings were substantiated by Stavraky<sup>7</sup> in anaesthetized animals. At the same time it was shown that mecholyl caused a marked secretion of pepsin and that it continued to stimulate the peptic cells after the inhibition of secretion of acid had set in.

In spite of a considerable amount of work done, the effects of the less stable choline esters, particularly those of acetylcholine, on gastric secretion are not as clearly established as those of mecholyl. Rapid destruction of acetylcholine in the blood stream usually necessitated preceding eserization which obscured the results. Even when eserine was not used, side effects of acetylcholine on the systemic circulation and on other organs considerably complicated the findings. In view of this, an attempt was made by one of us, Stavraky<sup>8</sup>, to develop a method of injecting acetylcholine directly into the gastric arteries. This method permitted a study of the effect of acetylcholine on gastric secretion uncomplicated by eserization or systemic effects. In addition, the method was found useful in the comparative study of the response of different regions of the stomach to acetylcholine. Some of the physiological results obtained with this method as well as the histological changes in the gastric mucosa following the intraarterial injection of acetylcholine will be made the subject of the present communication.

### METHODS

#### *A. Physiological*

In all, over forty sacrifice experiments were carried out on dogs anesthetized with a mixture of chloralose and urethane (3:1 to 8:1); chloralose alone and occasionally avertin or nembutal were used in control experiments. Preceding the experiment, the animals were kept on a liquid diet for 24 hours, and on water only for 24 hours. Tracheotomy, section of the vagi, and ligation of the

esophagus in the neck were carried out in the usual manner. Through a mid-line incision the spleen was exteriorized; the splenic artery freed from the mesentery and stripped of the surrounding nerve plexus for a distance of about one inch, the nerves being resected; a metal cannula was placed into the splenic artery in one of the three positions indicated in Fig. 1. Next, the pylorus was ligated at the sphincter, a cannula placed into the stomach and the abdominal incision sutured around it. Before closing the abdomen the cannula in the splenic artery was connected through a stab wound in the left flank with a burette which contained the solution to be injected. The solution was warmed to body temperature. The injections were carried out by manual opening of the tap on the burette or by an automatic clamp. In both instances the pressure for the intraarterial injection was obtained from a pressure bottle attached to the burette and containing the same solution as the latter. The duration of the injections ranged from 5 to 20 seconds and they were repeated once every 5 to 60 seconds. Variations in the duration of the injections as well as in the height at which the pressure bottle was placed made it possible to modify the amount of the injected drug without discontinuing the injection. By means of interchangeable pressure bottles the strength of the solution injected could be varied. Prolonged interruptions in the injections necessitated the placement of a curved arterial clip on the splenic artery in order to prevent the blood from clotting in the arterial cannula. This was resorted to as infrequently as possible.

The pH of the secretion was determined by means of the glass electrode. The free and total acidity were determined by titration with N/50 NaOH in the presence of Topfer's reagent and phenolphthalein respectively. The acid combining power of alkaline samples was determined by heating 0.5 cc. of gastric juice with 5.0 cc. of N/50  $\text{H}_2\text{SO}_4$  in a hot water bath and back titration with N/50 NaOH to methyl red. Pepsin was determined by the Nirenstein and Schiff<sup>9</sup> modification of the Mett's method and the chlorides by Wilson and Ball's<sup>10</sup> modification of Van Slyke's technique. Calcium was measured in control experiments by the Tisdall and Kramer<sup>11</sup> method.

### B. *Histological*

At the termination of the experiment the stomach was removed in toto and opened along the lesser curvature. A large block of mucosa was immediately cut from the central part of the stimulated area and divided in two. One half was fixed in 70% alcohol, imbedded in paraffin, sectioned at  $5\mu$  and stained with mucicarmine-hematoxylin according to Bensley's<sup>12</sup> technique. These sections were used for a study of the mucus secreting cells. The other half of the block was fixed in Regaud's solution and imbedded in celloidin paraffin according to Romeis's<sup>13</sup> technique. It was then sectioned at  $5\mu$  and stained

with neutral gentian as suggested by Bowie<sup>14</sup> for the study of pepsinogen granules. Sections fixed by this latter technique were also stained with hematoxylin-eosin for a general study of the gastric mucosa.

A second block of mucosa was cut from a quiescent area of the stomach along the greater curvature. This block too was divided and the halves fixed and stained as described above. In control experiments a block of resting gastric mucosa was removed at the beginning of the experiment when the cannula was being inserted into the stomach. When sections of this block were compared with sections cut from a quiescent area of mucosa taken at the end of the experiment (from a non-injected portion of the stomach), no detectable histological change could be noted and in subsequent experiments either procedure was used.

## RESULTS

### (A) Physiological:—*Observations on the secretion induced by the intra-arterial injection of acetylcholine into different regions of a quiescent stomach*

As shown in table 1, when injected into a completely quiescent stomach acetylcholine had a tendency to evoke diverse responses from different regions of the stomach. Injections directed into the region of the lesser curvature (Fig. 1 C) resulted mostly, after a latent period of 10 to 20 minutes, in a secretion of gastric juice of relatively low acidity but of very high digestive power and containing large quantities of mucus. Small quantities of a dilute concentration of acetylcholine stimulated the secretion of more highly acid gastric juice containing free hydrochloric acid. Larger quantities and stronger concentrations of acetylcholine increased the margin between free and total acidity often leading to complete disappearance of free hydrochloric acid from the secretion. When these injections were continued, they markedly reduced the total acidity of the secretion as well as the concentration of total chloride in it. However, the pH of the secretion stayed on the acid side and the digestive power of the secretion and the amount of mucus in it remained high even when quite excessive amounts of acetylcholine were introduced. Very large quantities of acetylcholine often inhibited not only the secretion of acid but reduced the total volume of the secretion as well.

Injections of acetylcholine directed through the gastrosplenic artery into a limited area of the body of the stomach along the greater curvature (Fig. 1 B) resulted usually in an abundant flow of alkaline secretion. When very dilute concentrations of acetylcholine were injected, occasionally, after a long latent period, an acid secretion appeared but it did not contain any free hydrochloric acid and it was not sustained, the pH shifting after 15–30 minutes to the alka-

line side. The secretion was mostly liquid but some surface mucus was present in it and, as judged by the viscosity of the secretion, it contained variable quantities of dissolved mucin. As long as the secretion was on the acid side it contained some pepsin, but as soon as the pH rose above 7.0 the pepsin abruptly disappeared from the secretion. The injection of larger quantities of more concentrated acetylcholine resulted from the start in an abundant flow of alkaline secretion which contained no pepsin. With proper concentration

TABLE I

*Composition of the secretion obtained on intra-arterial injection of acetylcholine into regions along the greater and lesser curvatures of the stomach (dog)*

	SECRETION FROM REGION OF GREATER CURVA- TURE. (POSITION OF ARTERIAL CANNULA INDI- CATED IN FIG. 1-B.)	SECRETION FROM REGION OF LESSER CURVA- TURE. (POSITION OF ARTERIAL CANNULA INDI- CATED IN FIG. 1-C.)
1. Number of experiments	28	8
2. Range of effective quantity of acetylcholine (mg./hr.)	0.3-96.0	2.8-80.0
3. Range of effective concentration of acetylcholine (mg./ml.)	0.002-0.4	0.01-0.4
4. Maximum rate of secretion $\frac{\text{ml.}/\text{hr.}}{\text{ml.}/\text{cm.}^2 \text{ hr.}}$	$\frac{98.8}{4.86}$	$\frac{100}{1.28}$
5. Range of pH	6.3-8.9*	—
6. Range of titrable acidity—Free/Total (mN)	$\frac{0.0-0.0}{0.0-15.2}$	$\frac{0.0-45.6}{12.6-78.0}$
7. Maximum titrable alkalinity—acid combining power (mN)	44.8	—
8. Pepsin activity (Mett's Units)	0-27	164-502
9. Total Cl (meq./l)	94.5-144.3	127.2-145.8
10. Ca (mg./100 ml)	23.2-7.7†	—

\* pH 8.9 given as the upper range of the alkaline secretion was encountered only in one experiment out of 57 in which acetylcholine was injected, and it is felt that a more representative value for the upper range of the pH of this secretion would be between 8.6 and 8.7.

† The upper level of calcium in the alkaline secretion is given as 23 mg./100 ml. However, this was true only of the initial samples of the secretion and sustained upper values for calcium during the height of the secretion ranged around 13.6 to 13.2 mg./100 ml.

of acetylcholine and with very little urethane in the anaesthetic mixture, the secretion was opalescent but colorless. When excessive amounts of acetylcholine were injected, samples collected later in the experiment often became tinged with traces of blood, this being facilitated by many anaesthetics, particularly by urethane but not by chloralose. If the amounts of acetylcholine were further increased, usually an inhibition of the secretion resulted during the period of the injection and the flow of gastric secretion took place during the after-effect. When the injection of acetylcholine was discontinued, the secretion rapidly declined and usually stopped entirely within 15-30 minutes.

Successive reintroductions of acetylcholine again caused a rapid flow of alkaline secretion after a greatly shortened latent period.

Injections of acetylcholine into the pyloric region of the greater curvature were carried out in 4 experiments (Fig. 1 A): the secretion from this region was relatively scanty but did not materially differ from the alkaline secretion of the body of the stomach, however, it did seem to contain some dissolved mucus which was not opalescent but clear.

*Effects of eserine and atropine:* Eserine injected in small quantities subcutaneously, intravenously, or intraarterially, greatly increased the sensitivity of the gastric glands to intraarterial injections of acetylcholine. This

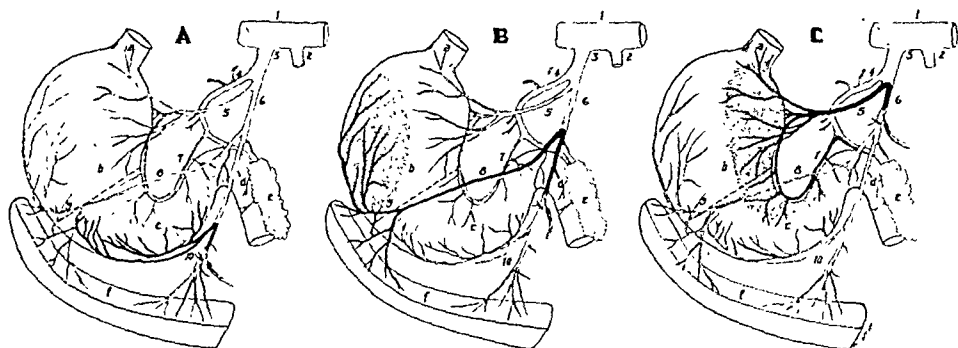


FIG. 1. SHOWS THREE POSITIONS OF CANNULA IN THE SPLENIC ARTERY AND RESULTANT INJECTIONS OF DIFFERENT REGIONS OF THE STOMACH

a) Esophagus b) body of stomach c) pyloric portion of stomach d) duodenum e) pancreas f) spleen.  
1. abdominal aorta 2. superior mesenteric artery 3. coeliac artery 4. hepatic artery 5. left gastric artery  
6. splenic artery 7. right gastric artery 8. gastrosplenic artery 9. left gastroepiploic artery 10. right gastroepiploic artery.

potentiating effect of eserine was prominent both in the case of acid and alkaline secretion. Not only did 100 to 500 times smaller amounts of acetylcholine cause a secretion, but also the inhibition of secretion caused by excessive doses of acetylcholine occurred with much smaller quantities of acetylcholine after previous eserinizaton. Excessive quantities of eserine injected intravenously or intraarterially caused a gastric secretion by themselves.

Atropine abolished or greatly diminished the secretion caused by acetylcholine from the region of both the greater and the lesser curvature of the stomach, but, when after atropinization the amounts of acetylcholine were increased 100 times or more, the effect of atropine could be partially overcome and a small secretion reestablished. However, even with these excessive quantities of acetylcholine the secretion never attained the previous level.

(B) Histological:—*Changes in the gastric mucosa resulting from the intraarterial injection of acetylcholine into different regions of a quiescent stomach*

The fact that the intraarterial injection of acetylcholine into the gastrosplenic artery evoked an abundant alkaline secretion raised the question as to the cellular elements of the gastric glands which could contribute to this secretion. A summary of the physiological results obtained in 11 sacrifice experiments conducted for the histological study is presented in table 2.

The region of the gastric mucosa which was stimulated by acetylcholine was confined to the area of distribution of the gastrosplenic artery. This included the fundus and the greater curvature portion of the corpus of the stomach (Fig. 1 B). Sections taken from this area, when stained with mucicarmine,

TABLE II

*Summary of the physiological aspects in experiments involving a histologic study of the gastric mucosa in the region of the body of the stomach along the greater curvature*

NUMBER OF EXPERIMENTS	DURATION OF EXPERIMENTS	ACETYLCHOLINE INJECTED INTO GASTROSPLENIC ARTERY	VOLUME OF SECRETION	pH OF SECRETION	PEPSIN ACTIVITY OF SECRETION
	<i>hrs.</i>	<i>mg./hr.</i>	<i>ml./hr.</i>		<i>Mett's Units</i>
11	4-6	4-10	14.2-98.8	8.0-8.6	0.0

presented a striking contrast when compared with similarly stained sections of quiescent mucosa (Fig. 2 A & B).

As shown in Fig. 3A, the chief cells of the neck in the quiescent mucosa contained an abundance of the mucous precursor in the form of closely packed pink-staining granules. The mass of secretory granules occupied the entire cell except for the basilar portion which contained the nucleus. In many cases the secretory mass appeared to have compressed the nucleus against the base of the cell with the result that the nucleus was oval in shape. In the sections taken from the injected (stimulated) area of the stomach (Fig. 3 B), the chief cells of the neck showed complete exhaustion of the secretory granules. For the most part the nuclei of these cells were more rounded and vesicular and were placed more centrally in the cells.

The cells of the surface epithelium similarly showed evidence of secretory activity after prolonged injection of large quantities of acetylcholine. As shown in Fig. 4 A, in a quiescent state these cells were packed with granules of the mucous precursor which appeared to have crowded the nucleus against the basilar part of the cell membrane. No clear cytoplasm was seen about the nucleus. The cells of the surface epithelium from an injected (stimulated) area



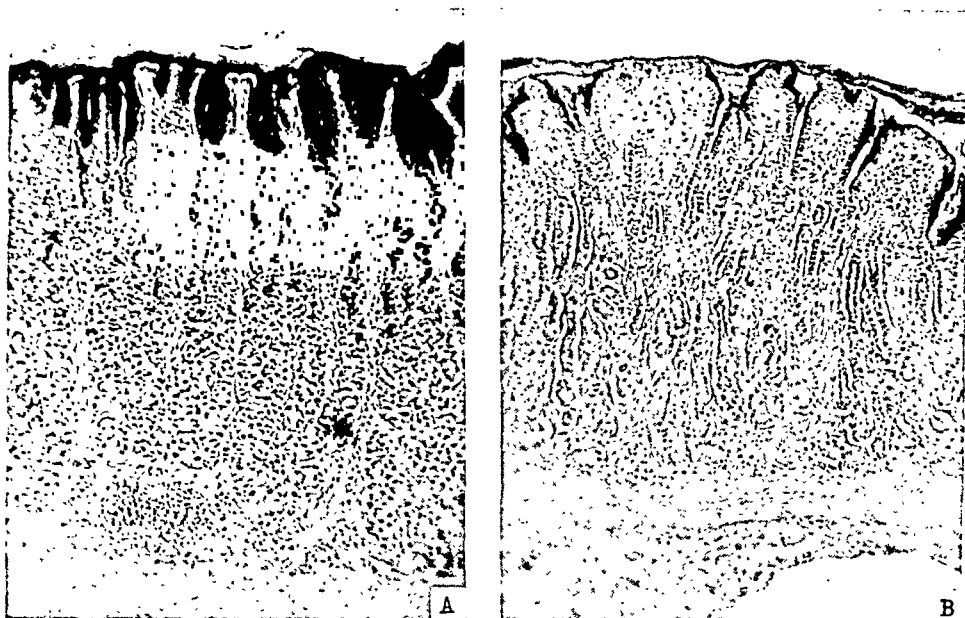


FIG. 2. General appearance of gastric mucosa in mucicarmine-hematoxylin stain. G and H filter. 109 $\times$ . a) Quiescent area. b) Injected area.

FIG. 2, 3 and 4. Show microphotographs of the gastric mucosa of dog (10.8 kg. body weight) before and after stimulation by means of injection of acetylcholine chloride into the gastrosplenic artery. Acetylcholine in 1/50,000 dilution (31.2 mg. in 4 hrs. injected at variable rate) evoked 383 ml. of alkaline secretion (4.86 ml./cm.<sup>2</sup>/hr.).

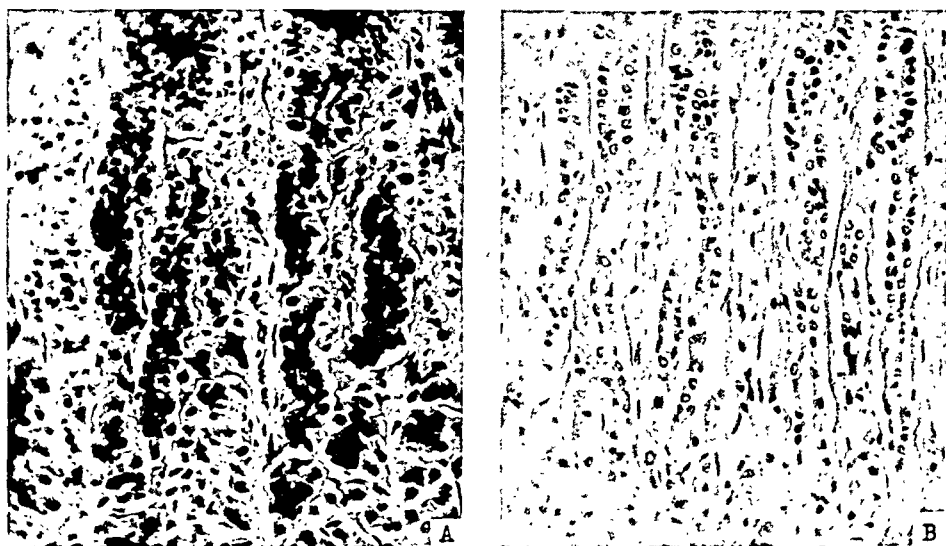


FIG. 3. Appearance of the chief cells of the neck of the gastric glands. Same stain. 300 $\times$ . a) Quiescent area. b) Injected area.

of the stomach (Fig. 4 B) contained less of the mucous precursor as evidenced by the fact that the masses of secretory granules occupied only the outer one-half to one-quarter of the cells. Between the secretory masses and the nuclei,

areas of clear cytoplasm could be seen. The nuclei did not appear to be crowded against the cell bases. These changes were most marked in the cells of the surface epithelium which line the depths of the gastric pits. In this location complete exhaustion of the mucous precursor was the rule. Proceeding from the cells of the surface epithelium which line the depths of the gastric pits to those which line the free surface of the stomach there was a gradual diminution in the degree of exhaustion exhibited by the cells.

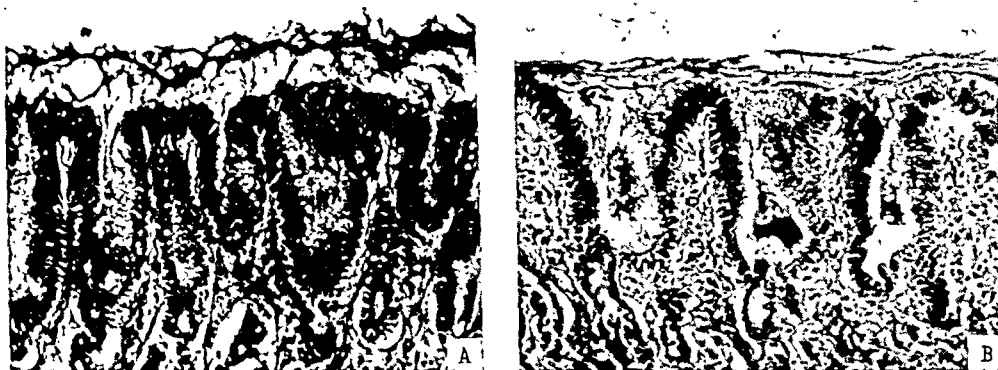


FIG. 4. Appearance of the surface epithelium. Same stain. 300 $\times$ . a) Quiescent area. b) Injected area.

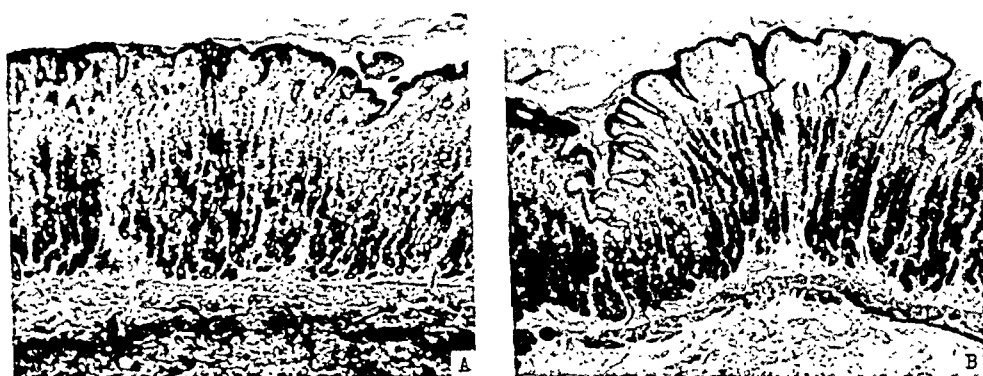


FIG. 5. Appearance of the chief cells of the body of the glands. Neutral gentian stain. Yellow-green filter. 54 $\times$ . (another animal). a) Quiescent area. b) Injected area.

Figs. 5 A and 5 B show the pepsinogen granules stained in representative sections taken from quiescent and injected (stimulated) areas of the gastric mucosa respectively. The neutral gentian stain was taken up by the pepsinogen granules of the chief cells of the body of the gastric glands, these cells standing out as blue-black granules. A comparison of the two sections showed that there were equally as many pepsinogen granules in the chief cells of the body in the section from the injected (stimulated) area as in those in the section from the quiescent area of the gastric mucosa. It would appear therefore

that these cells have not been stimulated to secrete by the intraarterial injection of acetylcholine.

A study of the parietal cells in the sections taken from the injected (stimulated) area and stained with hematoxylin-eosin revealed no demonstrable cytological change in these cells when they were compared with the parietal cells in similarly stained sections of the quiescent mucosa.

## DISCUSSION

### *Physiological*

In general, the intraarterial injection of acetylcholine into various regions of the stomach resulted in a secretion of low acidity. However, the gastric juice secreted from the region of the lesser curvature did contain free hydrochloric acid and when the quantities and dilutions of acetylcholine were carefully regulated, the secretion of free hydrochloric acid was sustained throughout the experiment. When excessive quantities of acetylcholine were introduced, free hydrochloric acid disappeared from the secretion but the reaction of the secretion still remained acid and the digestive power of the gastric juice was high.

Injections of acetylcholine into the region of the body of the stomach along the greater curvature resulted, even with minimal amounts of acetylcholine only in an initial secretion of hydrochloric acid. Later in the experiment the hydrochloric acid disappeared altogether from the secretion, the latter becoming alkaline in reaction. Simultaneously with this change in the pH of the gastric juice, the secretion of pepsin ceased abruptly. When excessive quantities of acetylcholine were injected from the start, the initial phase of acid secretion was not seen at all; the secretion being alkaline and free from pepsin throughout the experiment. As shown by Gray and Ivy<sup>5</sup> and confirmed in the present study, excessive quantities of acetylcholine undoubtedly do inhibit the secretion of hydrochloric acid. It is also known that the region of the lesser curvature of the stomach is richer in nervous elements than the region of the greater curvature (Brandt<sup>15</sup>, Schabadasch<sup>16</sup>) and even under the influence of the usual stimuli it secretes a gastric juice of greater acidity than other regions of the stomach (Alley<sup>17</sup>, Davidov<sup>18</sup>). Thus it could be argued that when the secretion of hydrochloric acid is depressed, it should disappear first from the regions of the stomach which respond by a less acid secretion under normal conditions. Besides excessive quantities of acetylcholine, among the conditions which may contribute to the general depression of the acid-secreting mechanism of the stomach, handling of the viscus and operative trauma should be considered. It has been shown by Babkin and co-workers<sup>19</sup> that such procedures lead to a prolonged depression of the secretory mechanisms which they

attributed to a reflex stimulation of the sympathetico-adrenal system. This could conceivably result in inhibition of the secretion of acid and pepsin particularly from the more handled portions of the stomach.

Another possible explanation of the difference in the response of the regions of the greater and lesser curvatures of the stomach may be that the injection of acetylcholine along the lesser curvature always involved the pyloric mucosa, whereas along the greater curvature it was localized to the body of the stomach. Uvnas<sup>20</sup> contends that vagal stimulation of the pyloric part of the stomach has a reinforcing effect upon the action of the vagi nerves on the rest of the gastric glands. Although, as shown by Babkin et al.<sup>19</sup>, Uvnas' concept is untenable in its entirety, this mechanism may play a part in the present experiments.

The inter-relation of the secretion of acid and pepsin is of interest. It is usually assumed that the secretion of these two components is independent of each other. In the present experiments however, the disappearance of acid from the secretion and a shift in the pH of the secretion to the alkaline side was accompanied by an abrupt disappearance of pepsin, the latter never being present in alkaline secretion. The alkaline secretion obtained from the region of the greater curvature on injection of acetylcholine compared well in its characteristics with the mucus studied by Hollander and co-workers<sup>21</sup> as far as the pH, total chloride, and other properties are concerned; also the calcium content of this secretion compares well with that described by Hollander and Lauber<sup>22</sup> in gastric mucus. It is true that due to the technique of sacrifice experiments, the resting samples and the initial acetylcholine samples often contained more calcium than usually found in the gastric secretion. However, on prolonged injection of acetylcholine, the calcium declined and sustained values for it in the alkaline secretion ranged between 13.6 and 9.2 mg./100 ml.

The fact that the effect produced by the intraarterial injection of acetylcholine was augmented by eserine and inhibited by atropine is in keeping with the current concept of the action of acetylcholine. It is interesting to note that the bloody tinge often present in the alkaline secretion evoked by acetylcholine from the region of the greater curvature was quite markedly reduced by atropine. This is in keeping with the view of Gray<sup>23</sup> that atropine reduces the permeability of the secretory elements of the stomach.

Perhaps the most striking feature of the alkaline gastric secretion was its large quantity. Despite the fact that it was obtained by artificial stimulation of the gastric glands it indicates the capabilities of the glandular elements by which it is secreted. The diluting and neutralizing potentialities of such a secretion may play a more prominent role in the control of gastric acidity than previously anticipated.

*Histological*

The unusual finding that on injection of acetylcholine into the gastrosplenic artery large quantities of alkaline secretion occurred from the region of the greater curvature of the body of the stomach raised a question as to the cellular elements which participated in this process. While it was shown by Bowie and Vineberg<sup>24</sup> that strong stimulation of the vagi nerves caused an exhaustion of the chief cells of the body of the gastric glands, Jennings and Florey<sup>25</sup> found that weak electric stimulation of the vagi caused predominantly exhaustion of the chief cells of the neck of the glands and attributed the secretion of mucus to the activity of these cells. Jennings and Florey<sup>25</sup> did not observe any change in the surface epithelium in their experiments. Later, on physiological grounds, the secretion of mucus by the surface epithelium was ascribed by Ivy<sup>26</sup> to a mechanical stimulation associated with motility. In our experiments, injection of acetylcholine into the gastrosplenic artery caused predominantly an exhaustion of the chief cells of the neck of the glands without any change in the cells of the body of the glands, and it is very likely that the chief cells of the neck contribute mostly to the alkaline secretion described above. However, with the present technique there was seen some exhaustion of the surface epithelium as well, and the question arose whether changes in the surface epithelium were due to the motility or whether acetylcholine in the large quantities employed had some direct action upon them: two considerations tend to favour the latter possibility. When the results of experiments were compared in which the duration of the injection of acetylcholine was kept to four hours but the quantity of acetylcholine varied, the amount of the secretion during that period of time differed with the quantity of acetylcholine introduced into the gastrosplenic artery. In the group of experiments in which the amount of secretion was equal to 4.86 ml./cm<sup>2</sup>./hr. there was quite a marked exhaustion of the surface epithelium during the four hour period of injection of acetylcholine. In experiments in which during the four hour injection of acetylcholine the rate of secretion averaged 2.3 ml./cm<sup>2</sup>./hr. the exhaustion of the surface epithelium was only moderate but definitely present; in experiments in which the secretion was less than 2 ml./cm<sup>2</sup>./hr. in spite of a similar duration of the injection of acetylcholine (4 hours) there was no detectable exhaustion of the surface epithelium. Though not studied separately, the gastric motility caused by the injection of acetylcholine seemed to have been more or less the same in all these experiments and as it lasted in all of them the same period of time, its effect should have been the same on the surface epithelium. A second consideration in favor of a specific action of acetylcholine is that the activity in the surface epithelium was usually observed in the crypts and not on the surface of the mucosa, whereas motility should cause greater irritation

of the surface layers than those lying deep in the crypts. However, in the absence of a direct investigation of the part played by the motility in the action of acetylcholine on the surface epithelium of the stomach it is felt that no definite opinion regarding this question should be expressed at this stage of the work.

#### SUMMARY AND CONCLUSIONS

1. A method of intraarterial injection of acetylcholine into various regions of the stomach of the dog is described. When injected into a quiescent stomach acetylcholine evokes diverse responses from different regions of the viscus. Introduced into the left gastric artery (region of the lesser curvature) acetylcholine causes a secretion of low acidity but containing large quantities of mucus and pepsin. For the most part free hydrochloric acid is absent from the secretion and the total chloride is low. Injected into the gastrosplenic artery (body of stomach along the greater curvature) acetylcholine causes an abundant flow of an alkaline secretion. This sometimes follows an initial period of acid secretion. The alkaline secretion (pH 7.6–8.9) contains variable amounts of dissolved, opalescent mucus but no pepsin and the total chloride in it varies between 94.5 and 144.3 m.eq./l. Also from the pyloric region of the stomach (injections into the right gastroepiploic artery) acetylcholine evokes a secretion of alkaline mucus; the latter, however, being not opalescent but clear.

2. A histological study of the mucosa of the injected regions of the stomach shows that when acetylcholine is introduced into the gastrosplenic artery during a period of 4 to 6 hours (injection of a limited area of the body of the stomach along the greater curvature resulting in an alkaline secretion) complete exhaustion of the chief cells of the neck of the gastric glands and partial exhaustion of the surface epithelium takes place. In contradistinction to this, the chief cells of the body of the glands are found to contain large numbers of pepsinogen granules showing no difference between the injected and the resting mucosa.

3. It is concluded that the alkaline secretion which results from injections of acetylcholine into the gastrosplenic artery comes from the inner one-third of the glands of the body of the stomach along the greater curvature, the chief cells of the neck and possibly the surface epithelium contributing to this secretion.

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# THE THREE MAIN COMPONENTS OF THE HUMAN GASTRIC MUCIN: DISSOLVED MUCOPROTEOSE, DISSOLVED MUCOPROTEIN, AND MUROID OF THE GASTRIC VISIBLE MUCUS

## PART I. DIFFERENTIATION; SOME PHYSICAL AND CHEMICAL CHARACTERISTICS; CLASSIFICATION

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### INTRODUCTION

As far as gross appearance is concerned, gastric mucin is said to occur as "visible (surface epithelium) mucus" and as "dissolved mucin" (muroid secretion). The first is a jelly-like, colorless, transparent, tenacious material which adheres closely to the mucosa; it forms shreds or lumps when precipitated in acid gastric contents. The second is a mucous substance which is dissolved in and intermixed with other components of gastric juice upon which it confers the property of viscosity. The fundamental question of whether visible mucus and dissolved mucin are two distinct products secreted by particular cells (dualistic theory) or whether the columnar cells of the surface epithelium, the neck cells of the glands of the fundus and the body, as well as the muroid cells of the cardiac and pyloric glands all secrete both components (unitarian theory) has received different answers.

Disagreement also prevails in respect to the significance of differences in the histologic structure of cells secreting gastric mucin. Since the neck cells give histochemical reactions different from those of the surface epithelium and of the pyloric and cardiac glands<sup>1, 2</sup> Lim would limit the name "muroid" to the neck cells and would distinguish them from the columnar cells of surface epithelium and from cells of the pyloric and cardiac glands. Others would apply the term "muroid" to all mucosal cells secreting gastric mucin since they are oxyphilic<sup>3</sup>; the basophilic goblet cells of the intestine which also secrete mucus would then be assigned to the "mucous" cells. Babkin<sup>4</sup> considers the evidence that histochemical differences prove a difference in the chemical composition of mucus inconclusive. Moreover the physico-chemical characteristics of mucus might be affected by the intensity and type of the physiologic or pharmacologic stimulus responsible for its secretion<sup>5</sup>.

Chemical analyses have also not fully resolved the problem of a single versus multiple components of mucus. It is known that visible, surface epithelium mucus contains 12.2% nitrogen, 31-35% reducing substance, and 2% ash<sup>6</sup>; a neutral mucopolysaccharide containing acetylglucosamine and galactose in a ratio of 1:1 has been isolated from the visible mucus of the hog stomach<sup>7</sup>. In addition some information on the pH, alkalinity, buffering capacity and electrolytic content of visible



mucus has been obtained<sup>8-14</sup>. On the other hand, "dissolved mucin" is said to be a mucoprotein containing mucoitinsulfuric acid; its reducing power corresponds to 12.6-12.8% glucose only; it contains, on the average, 13.8% nitrogen and 0.2% ash and seems related to pepsin<sup>6</sup>, as well as to the erroneously named "gastroglobulin"<sup>15</sup>. Its low nitrogen content and the presence of a reducing substance indicate that the compound is not identical with pepsin although their crystals are similar<sup>15</sup>. A closely related mucoïd containing sulfomucopolysaccharide acid has been isolated from the gastric mucosa of the hog<sup>16</sup>; it contains acetylglucosamine, sulfuric acid, and non-defined uronic acid.

No further data on this subject is available. In the absence of a definite conclusion, several alternatives concerning the origin of dissolved mucin have been suggested<sup>4</sup>: 1) it originates from the partial dissolution of surface epithelium mucus on standing; 2) it is a soluble fraction of surface epithelium mucus; 3) it is derived from the pepsin-hydrochloric acid digestion of surface epithelium mucus; 4) it is secreted as such or in combination with pepsin by the mucoïd neck cells of the gastric glands.

#### HETEROGENEITY OF THE DISSOLVED GASTRIC MUCIN

Studies of gastric mucin by our iodometric method<sup>17, 18</sup> and during the development of the tyrosine method for determination of total dissolved gastric mucin<sup>19, 20</sup> have led us to the conviction that visible mucus and dissolved mucin chemically are different compounds. What is more important, we learned that the dissolved mucin also is not an entity but rather a heterogeneous mixture of at least two substances. On this essential fact all our further inferences and studies are based.

In this work we employed the principle of double consecutive precipitation of the centrifuged and filtered fluid gastric juice with a half-volume of 10% trichloroacetic acid and one and one-half volumes of acetone. In this concentration trichloroacetic acid precipitates almost all contaminants of the gastric juice (proteins derived from blood and food, salivary mucus, some mucous constituents of bile<sup>19</sup>) but the dissolved gastric mucin passes to the filtrate from which it may be precipitated with acetone.

In collaboration with Heisler and Drekter<sup>21</sup> we found that the mucin dissolved in the fasting juice of one person may differ from that obtained from the fasting gastric juice of another individual; further that radical differences are encountered depending upon the isolation of the dissolved mucin from an acid or from the acid gastric contents of the same person; finally, that the mucin isolated from the same person may exhibit different characteristics depending upon the type of stimulation employed. These differences concern many physical characteristics such as color, consistency, microscopic structure, degree of hydration, solubility in acids and salts, and extractability with 60% alcohol.

They also concern chemical differences, the tyrosine and nitrogen content, the reducing power as calculated by dry weight, for example.

These findings could be correlated in part with the observation of Komarov<sup>22</sup> who found that the dissolved mucin isolated from canine gastric juice after the injection of histamine had a slightly smaller content of nitrogen and 2-3 times more reducing substances than dissolved mucin obtained after sham feeding. While concluding that the mucin of histamine gastric juice is more akin to the compound recovered from visible mucus than to the dissolved mucin after sham feeding, the author draws no further conclusions and in his recent papers treats the dissolved mucin as an entity<sup>23, 24</sup>. According to our data, however, dissolved mucin of filtered gastric juice is a mixture of at least two different components and its physical and chemical characteristics depend upon the mutual ratio of these components in the "dissolved mucin" complex<sup>21</sup>.

Differences in solubility and precipitate formation makes it easy to separate these substances.<sup>21</sup> One component, previously dissolved in acid gastric juice, after precipitation with acetone from the trichloroacetic filtrate, loses its ability to remain in solution at a pH below 4 (near its isoelectric point). If this acetone precipitate is taken up with 0.1 N NaOH and enough acid is added to bring the pH below 4, the compound precipitates as extremely light, opal-colored flocculi. The second component of dissolved mucin, if treated in the same way, remains in solution and from this it may be reprecipitated, for the most part, with one or one and one-half volumes of acetone. These findings form the basis of the separation procedure for the isolation and study of these components. The chemical and physical features of these products are listed in Table 1, according to data published in cooperation with Heisler and Dreker<sup>21</sup>.

One of these substances has been called "*dissolved gastric mucoproteose*" because it possesses the features of a proteose and those of a mucoid substance.

The proteose-like features of this compound are: 1) It is soluble in low concentrations in water, salts and acids with which it forms colloidal solutions, and dissolves perfectly in dilute alkali; 2) it is incompletely precipitated by saturation with ammonium sulfate, and not precipitated by trichloroacetic acid, by zinc acetate solution, nor by heating; 3) it is precipitated with acetone and alcohol; 4) it is not dialysable<sup>18</sup>; 5) it gives a violet-purple biuret reaction; 6) shaken with 60% alcohol it goes partly into solution; 7) a very similar substance has been isolated from the enzymatic digestion product of the visible gastric mucus<sup>25</sup>.

The relation of this compound to the mucoids is evidenced by: 1) high content in reducing substances; 2) low content in nitrogen and tyrosine; 3) viscous, tenacious resin-like appearance after precipitation with acetone; 4) re-

TABLE 1

*Some physical and chemical data on the dissolved gastric mucoprotein, dissolved gastric mucoproteose, and the mucoproteose-like compound obtained from the mucoid of visible gastric mucus after enzymatic digestion*

PHYSICAL AND CHEMICAL CHARACTERISTICS	1 DISSOLVED GASTRIC MUCOPROTEIN FROM GASTRIC JUICE	2 A) DISSOLVED GASTRIC MUCOPROTEOSE FROM GASTRIC JUICE AND B) MUCOPROTEOSE-LIKE COMPOUND OBTAINED FROM VISIBLE GASTRIC MUCUS AFTER ENZYMATIC DIGESTION
Appearance of the acetone precipitate	Extremely light and flocculent, opal colored, floating to surface of .2N NaCl, very slowly desiccating in incubator	Heavy, clumping, brownish, resin-like, adhering to glass walls and very rapidly desiccating after washing with acetone
Appearance of the dried substance	Dirty grey crystalline particles resistant to crushing	Chalk-white substance easily crushing to an amorphous powder
Microscopic structure	Crystalline	Amorphous
Solubility of the acetone ppt. in acid/salt solution below pH 4	Insoluble	Soluble
Solubility in water, salt sol., and dilute acids	Insoluble	Soluble in low concentrations and forming turbid solutions
Precipitation with sat. ammonium sulfate	Yes	Incomplete
Precipitation with $\frac{1}{2}$ vol. 10% trichloroacetic acid	None	None
Precipitation with acetone	Yes	Yes
Solubility in alkali	Yes	Yes
Biuret reaction	Violet	Violet-purple or violet
Color yield on alkaline hydrolysis in low conc.	None	Yellow
Extraction with 60% alcohol	to 5%	to 40%
Degree of hydration as measured by dry substance content in 1 cc. of compound precipitated with acetone and centrifuged 5 minutes at 3000 RPM	Very large: 2% dry substance*	Small: 24.5% dry substance*

\* Mean value.

† Mean value with standard error.

TABLE 1—*Continued*

PHYSICAL AND CHEMICAL CHARACTERISTICS	1 DISSOLVED GASTRIC MUCOPROTEIN FROM GASTRIC JUICE	2 A) DISSOLVED GASTRIC MUCOPROTEOSE FROM GASTRIC JUICE AND B) MUCOPROTEOSE-LIKE COMPOUND OBTAINED FROM VISIBLE GASTRIC MUCUS AFTER ENZYMATIC DIGESTION
Tyrosine content in 1 cc. of compound precipitated with acetone and centrifuged 5 minutes at 3000 RPM	1.4 mg.*	10.0 mg.*
Tyrosine content (per dry weight of substance)	7.50 $\pm$ 0.65 mg. %†	3.9–4.2 mg. %
N content (per dry weight of substance)	12.61 $\pm$ 0.44 mg. %†	5.7–7.3 mg. %
Nitrogen/tyrosine ratio	1.64 $\pm$ 0.08†	1.4–2.0
Reducing substances before hydrolysis (glucose per dry weight of substance)	6.38 $\pm$ 1.48%†	about 16.0%
Reducing substances before hydrolysis to nitrogen ratio	0.50 $\pm$ 0.11†	over 2.0

covery of a similar substance from the mucoïd of the gastric visible mucus after enzymatic digestion or treatment with concentrated alkali<sup>25</sup>.

This substance has some resemblance to commercial gastric mucin obtained by peptic digestion from the gastric mucosa of the hog. The latter has the same low nitrogen content (about 7–8%), similar reducing power (25–35% after hydrolysis) and the same solubility and precipitation data. The dissolved mucoproteose is, however, not identical with commercial mucin for the latter is a digestion product of all mucous substances contained in the gastric mucosa of the hog.

Dissolved mucoproteose, in contrast to the second component of dissolved mucin, is not a chemical entity but a complex of intermediate products in the process of enzymatic digestion. For this reason the peptid moiety of this substance may show transitions between the first products of enzymatic disintegration of proteins (proteans, primary proteoses) and further split products (secondary proteoses or even peptones). The name "dissolved mucoproteose" is a simplification and stands for a complex of proteose-like split products of the gastric mucous substances formed under the influence of the local mucolytic enzymes.

The second component of the dissolved mucin complex has been called "*dissolved gastric mucoprotein*" since it is closely related to and probably identi-

cal with the compound originally isolated and described as "gastric mucoprotein" by Webster and Komarov.<sup>6</sup> The dissolved mucoprotein almost certainly is identical also with the "gastro-globulin" of Martin<sup>15</sup>; the mucopolysaccharide moiety of the mucoprotein is probably related to the acid mucopolysaccharide of Meyer and Smyth<sup>16</sup>.

#### ORIGIN OF VARIOUS MUCOUS COMPONENTS IN THE GASTRIC MUCOSA

In regard to the origin of *dissolved mucoproteose* the evidence shows its derivation from the visible gastric mucus, that is, from the surface epithelium cells.

There is a close similarity of the mucoproteose isolated from the filtered fluid gastric juice to the compound isolated by the same method from visible gastric mucus obtained during gastroscopy and subjected to enzymatic digestion. The similarity of the products is evident from Table 1. Small differences in the percentage of nitrogen, tyrosine, and reducing substances, calculated on a dry weight basis, exist<sup>25</sup> since the products of mucus digestion are intermediates which, according to the degree of disintegration, will vary in their composition.

Digestion of visible mucus in an incubator at 40°C does not require an acid milieu. Pepsin also does not appear to be indispensable for this digestion<sup>25</sup>. Moreover the digestion may proceed at pH of 8-9 at which the activity of pepsin is very slight, if it exists at all.

The formation of the dissolved mucoproteose from gastric mucus depends, in all probability, upon mucolytic enzymes in the gastric contents and, more specifically, upon those adsorbed or dissolved in surface epithelium mucus. These mucolytic enzymes may be related to lysozyme, the mucolytic action of which on the gastric and intestinal mucus has been suggested<sup>26, 27</sup>.

The existence of a mucolytic enzyme group, concerned with depolymerisation and hydrolysis of the neutral mucopolysaccharide fraction of gastric mucin was suggested by Meyer<sup>28</sup>.

The origin of the dissolved mucoproteose can be assigned to the surface epithelium cells of the gastric mucosa, if we accept the thesis that visible mucus originates from the surface epithelium; this seems almost certain. If, on the contrary, one assumes that all mucoïd cells of the stomach participate in the formation of visible gastric mucus and dissolved mucoproteose, from whence then comes the other mucous component, the dissolved mucoprotein? If, according to the unitarian theory, this is also secreted by the surface epithelium cells of gastric mucosa one should expect to find it in the visible mucus itself or its digestion products. Actually we<sup>25</sup> were unable to find more than small traces of dissolved mucoprotein in digested or in native mucus. These could easily have been adsorbed on the mucus in the same way as happens in the case of pepsin<sup>29</sup>.

Another fact favors the origin of the dissolved mucoproteose solely from the surface epithelium. The mucoproteose is found in all samples of the gastric contents, during fasting as well as after various types of stimulation and irrespective of acidity or anacidity (compare Part III). The surface epithelium, continuously secretes its product<sup>4</sup> while the gastric glands secrete rather intermittently. The constant presence of dissolved mucoproteose in gastric contents strongly indicates its origin from surface epithelium. A constant digestion of the mucus by mucolytic enzymes resulting in formation of mucoproteose is to be postulated in addition.

It is possible, however, that another compound, physically dissolved in the gastric juice also is secreted directly by the surface epithelium cells (or also mucoid cells of the cardiac and pyloric glands of the stomach) into the gastric lumen. This compound would be akin to the mucoid of the surface epithelium mucus and its digestion products and would be secreted in a soluble form without passing through the stage of gel-forming compound. This suggestion results from data discussed in Part III of this paper.

The second component of dissolved mucin, the *dissolved mucoprotein*, apparently is secreted, as was originally supposed by Webster and Komarov, by the mucoid cells of the gastric glands, most probably by the chief cells of the glands of the fundus and the body. The following facts support this thesis:

1) No appreciable amounts of mucoprotein are obtained from the mucoid of the surface epithelium, either after enzymatic digestion, or after treatment with concentrated alkali<sup>25</sup>.

2) The mechanism of mucoprotein secretion is very similar to that of another product of gastric glandular activity, i.e., pepsin. The secretion of both is greatly augmented by vagal stimulation and both show the same temporary increase (or "wash-out phenomenon") under the influence of histamine.

3) The compound is formed intermittently like all other secretions of gastric glands (hydrochloric acid, pepsin) and is absent or found only in small amounts in anacid fasting gastric contents.

4) The secretion of the dissolved mucoprotein is definitely related to the activity of parietal cells of the gastric glands, (Part III) and it accompanies the secretion of acid.

5) The compound is crystalline like pepsin (another product of gastric glands) and not amorphous like the mucoid of the visible mucus or dissolved mucoproteose.

6) The secretion of the mucoprotein is not prevented by subtotal gastrectomy. This operation leaves intact the glands of the fundus and of that part of the body which contains most of the mucoid neck cells.

DEFINITIONS; PHYSICAL AND CHEMICAL CHARACTERISTICS OF VARIOUS  
MUCOUS COMPONENTS OF GASTRIC ORIGIN

Knowledge of the physical and chemical properties of the various mucous components allows more precise physiological and clinical definition and classification of these bodies.

Formerly numerous confusing names were used by various authors to denominate the same mucous substance, or the same name was also applied frequently to define quite different mucous components. Terms such as "gastric mucin", "visible mucus", "surface epithelium mucin", "mucoid secretion", and a host of others are used arbitrarily and without fixed meaning.

The extent of prevailing confusion may be illustrated by the current usage of "gastric mucin". According to the terminology of the Council on Pharmacy of the American Medical Association, this is the name of the commercial preparation used for therapeutic purposes; it is obtained from the hog stomach mucosa by means of hydrochloric acid-pepsin digestion. This product contains a variety of mucous substances present in the stomach contents. Jones and Ivy<sup>30</sup> showed that it also contains many digestion products of a peptone character. The term "gastric mucin" denominates therefore the mixture of all mucous components of the stomach. This concurs with the opinion of Meyer<sup>31</sup> who states: "The term 'mucin' has only a physiological meaning, denoting a viscous secretion". On the other hand Hollander<sup>32</sup> calls mucin a distinct solid chemical substance of the class of conjugated proteins which forms one constituent of the mucous secretion proper. This definition is diametrically opposed to the preceding and identifies "mucin" with "dissolved mucin" of Komarov and Webster (therefore with mucoprotein); further examples of the extent of prevailing confusion could be cited.

On the basis of data available it is now possible to prevent further confusion by precise definitions of the mucous components derived from the gastric mucosa. This will enable their classification for physiological and clinical purposes.

We propose to use the term "*gastric mucin*" or "*total gastric mucin*" according to the suggestion of Meyer<sup>31</sup> only in the broad physiological sense to define the sum total of viscous secretion of the gastric mucosa as well as viscous products derived from enzymatic digestion of these secretions. This will also conform to the current name of the commercial product. The broad name of "gastric mucin", useful to physiologists and clinicians, therefore will include two chief components, each of which also has only a physiological and clinical meaning, i.e., A) "*dissolved gastric mucin*", and B) "*visible gastric mucus*".

A) As "*dissolved gastric mucin*", we understand the totality of the mucous substances of gastric origin or viscous products of their digestion which are

dissolved in the gastric juice, which are responsible for its viscosity, which cannot be separated from the gastric juice by filtration or centrifugation, but they can be isolated by precipitation with acetone or alcohol. No chemical meaning is attached to this term.

In the "dissolved mucin" complex we can at present distinguish with certainty at least two main components, each of them having special physical and chemical characteristics, i.e., 1) "*dissolved gastric mucoprotease*", 2) "*dissolved gastric mucoprotein*". They seem to be responsible for the viscosity of filtered gastric juice.

1) "*Dissolved gastric mucoprotease*" in dry form is a chalk-like whitish amorphous substance derived mainly from the enzymatic digestion of the mucoid of visible mucus. It is precipitated from the trichloroacetic acid filtrate of native gastric juice by acetone; if this precipitate is taken up with dilute alkali it may be re-precipitated by acetone but not by acid. The other known physical and chemical characteristics of dissolved gastric mucoprotease are listed in Table 1.

Dissolved mucoprotease, as will be discussed in Part III, is found in all human gastric contents, in anacid as well as in acid gastric samples, in fasting contents as well as after various types of stimulation.

Highest values are found in anacid fasting fluid contents of some cases of gastritis, in some gastric or duodenal ulcers, in gastric retention, and after vagotropic stimulation with some of the parasympathemimetic substances. Its concentration, in general, is higher than that of the dissolved mucoprotein, and, with our method, was found between 35 and 700 mgm. per 100 cc. of centrifuged fluid gastric juice.

Perhaps a similar soluble substance related to the mucoid of the gastric mucus is directly secreted by the surface epithelium cells of the stomach (or mucoid cells of the cardiac or pyloric glands) under the influence of vagal stimulation. The reasons for postulating such a mechanism of secretion will be discussed in Part III of this paper.

2) "*Dissolved gastric mucoprotein*", another component of the "dissolved mucin", is a well defined chemical substance. After precipitation with acetone from the trichloroacetic acid filtrate of the centrifuged gastric juice and taking up with dilute alkali it loses its solubility in salt-acid milieu below the pH of 4 and can be reprecipitated by addition of acid at this pH. The precipitate is very light, opal colored, flocculent and floats to the top of the tube containing 0.2N NaCl solution. After denaturation with acetone this substance is soluble only in alkali but not in water, salts or acids.

Dissolved mucoprotein in dry form has a dirty grey color. Bile pigment may be adsorbed to it, if mucoprotein is separated from gastric juice contaminated with bile. In this case it may show a dirty green tint. The mucopro-



tein is resistant to crushing and shows definite crystalline structures with polygonal base which, under the microscope, look like those shown in Fig. 1.

The other physico-chemical characteristics of dissolved mucoprotein are listed in Table 1.

Dissolved mucoprotein is found mainly in acid gastric juice, in fasting as well as after stimulation with alcohol and histamine. It is found in highest concentrations after vagotropic stimulation. It is almost absent or rarely found in the anacid fasting gastric contents. Its concentration ranges in the fluid

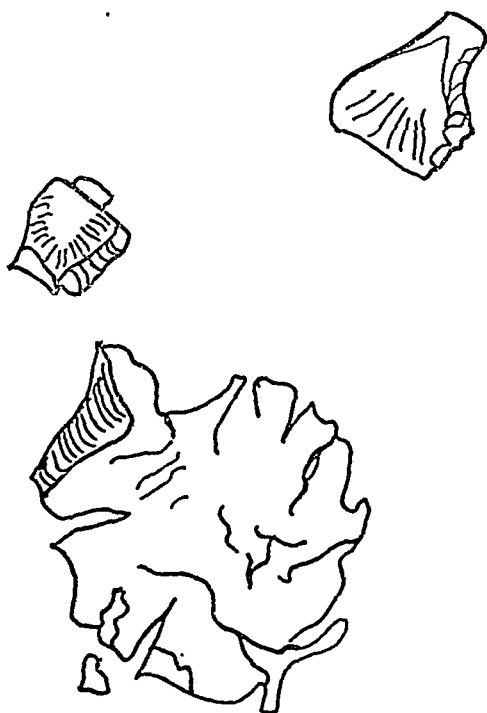


FIG. 1. CRYSTALS OF MUCOPROTEIN SEPARATED FROM HUMAN GASTRIC JUICE

gastric juice, as determined by the method to be described, between 0 and 460 mg. per 100 cc. of the centrifuged fluid gastric juice.

B) "*Visible gastric mucus*" is another chief component of the gastric mucin. This term, however, may be used only in a physiological or clinical sense; it has no chemical meaning whatsoever. It is a term for a) "*native gastric mucus*", i.e., jelly-like material found in the anacid stomach of man, transparent, more or less tenacious, sometimes almost fluid, which by agreement of histologists, physiologists and gastroscopists, should be considered largely a product of the surface epithelium cells of the gastric mucosa; b) "*precipitated gastric mucus*", i.e., shreds and lumps precipitated from native gastric mucus by hydrochloric acid of the stomach. Both these forms of the gastric mucus represent the "*vis-*

ible mucus" fraction of the gastric mucin. The chemically defined mucous compound responsible for the viscid property of the visible gastric mucus is a substance which we shall call here "*surface epithelium mucoid*" or better "*mucoïd of the visible gastric mucus*". The latter term is preferable, since it leaves to further investigation to what extent the mucoïd of the visible mucus may originate also from other secretory cells of the gastric mucosa (mucoïd cells of the cardiac and pyloric glands?).

3) "*Mucoïd of the visible gastric mucus*" or "*surface epithelium mucoid*" is the third chemically defined mucous component of gastric origin. This is the chemical substance responsible for the viscous quality of gastric mucus and gel formation. The "gastric mucus" is the final product of imbibition with water, apposition and adsorption of crystalloids, enzymes and cellular products to this mucoïd, which has the property to form a viscid gel.

The mucoïd of gastric mucus isolated by Meyer et al.<sup>7</sup> and mentioned earlier contains 75 per cent of the neutral mucopolysaccharide and 25 per cent of a peptid moiety.

According to our data<sup>25</sup> the alkaline mucoïd precipitates on addition of a half-volume of 10 per cent trichloroacetic acid. This precipitate contains, from 21 to 39 (average 30) mg. of tyrosine and from 58 to 64 (average 60) mg. nitrogen per 100 cc. of mucus.

On addition of acetone to the visible mucus, the mucoïd precipitates to form a rapidly shrinking and upward floating lump which contains on the average 87 per cent of the total tyrosine content of the mucus from which it is derived. On standing a little, more precipitate falls to the bottom and this contains about 13 per cent on the average of the total tyrosine content of the mucus<sup>25</sup>; it has the physical and chemical characteristics of the dissolved mucoproteose. This precipitate corresponds therefore either to dissolved mucoproteose adsorbed on the mucus or, what is more probable, to the first stage of enzymatic digestion of the visible mucus. The acetone precipitate of the surface epithelium mucoïd contains, on the average, about the same amount of tyrosine as is obtained by means of trichloroacetic acid precipitation. Our values were between 21 and 47 (average 36) mg. tyrosine and between 60 and 78 (average 69) mg. nitrogen per 100 cc. of mucus. Since the nitrogen content of the visible mucus, calculated per dry weight, averaged 7.0 per cent in our determinations<sup>25</sup>, the content of mucoïd in visible mucus calculated per dry weight is less than 1 per cent. This shows the extent of hydration of this gel-like material.

The ratio of reducing substances to nitrogen content in the mucoïd of the visible mucus, precipitated with acetone or trichloroacetic acid, ranges<sup>25</sup> between 1.3 and 3.6 (average 2.3) without hydrolysis and between 3.5–8.0 (average 6.2) after acid hydrolysis. Since the nitrogen content of the mucoïd of

visible mucus, calculated per dry weight, averaged 7.0 per cent (similar to commercial mucin) the content of reducing substances in the mucoid of visible mucus, calculated per dry weight will average 16.1 per cent, if determined without hydrolysis, and 39.2 per cent after acid hydrolysis. This value for reducing substances is very close to that found in dissolved mucoproteose and indicates again the origin of the latter substance from the surface epithelium mucus. It is also similar to the data of Webster and Komarov<sup>6</sup> who found an average of 35 per cent of reducing substances after hydrolysis in the surface epithelium mucus of the dog.

Under the influence of enzymatic digestion visible mucus liquefies and precipitation no longer occurs when trichloroacetic acid is added in the usual concentration (half-volume of 10 per cent solution). In the initial period of digestion the addition of acetone to the trichloroacetic acid filtrate of visible mucus causes a typical, rapidly shrinking and upward floating lump of precipitated mucoid of the visible mucus to form. This explains why in some filtered gastric contents, the addition of acetone to the trichloroacetic acid filtrate causes this precipitate as well as that of dissolved mucin. It means that in the filtered gastric juice of this individual some early products of digestion of visible mucus are present; these are closely related to the dissolved mucoproteose and are determined by the tyrosine method for the dissolved mucoproteose fraction.

On more complete digestion, no precipitate of this kind forms and the acetone precipitate has all the characteristics of the precipitate of dissolved mucoproteose described in Table 1.

On addition of concentrated alkali (sodium hydroxide in a final concentration of 1N solution) the mucus dissolves and the mucoid changes and loses its property of precipitation with trichloroacetic acid. Probably this is due to the depolymerizing action of concentrated alkali on the polysaccharide group of the mucoid. Also the addition of acetone directly to the digested mucus does not cause precipitation in the form of the floating mucus lump. Rather the material has all the characteristics of the "mucoproteose precipitate"<sup>25</sup>.

The similarity of the final effect of concentrated alkali on the visible gastric mucus and enzymatic digestion is striking. This finding is utilized for the quantitative determination of the mucoid of the gastric mucus (Part II).

#### CLASSIFICATION OF MUCOUS SUBSTANCES OF GASTRIC ORIGIN

A classification of the main mucous components derived from the gastric wall and found in the gastric contents is suggested in Figure 2. This classification utilizes the new information available in regard to the chemically defined mucous substances and retains the useful physiological and clinical terms which have no chemical implication. The relative position of these terms is shown whereby the chemically defined compounds are printed in capitals and

enclosed in boxes formed by thick solid lines. Those used only in a physiological or clinical sense are printed in small letters and enclosed in boxes formed by broken lines. The probable place of origin of the mucous compounds is shown in boxes framed by double solid lines. The mechanism of origin is written along or across the arrows, which show the place of origin of these substances. The more important mechanisms of origin are shown by means of thick lines. The relation of the chemically defined substances to the physiological and clinical terms is shown by means of broken lines.

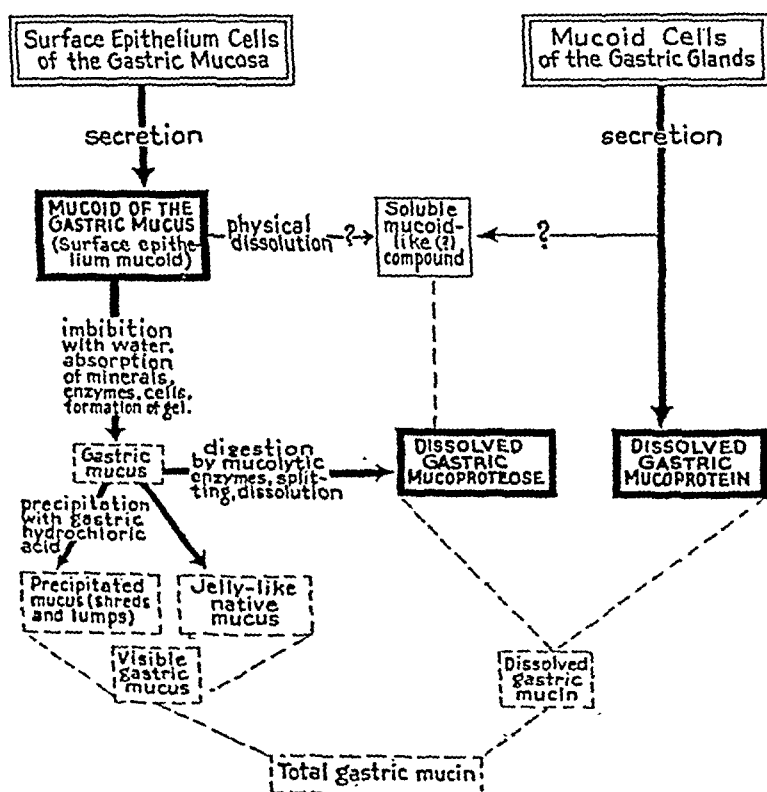


FIG. 2. CLASSIFICATION AND MECHANISM OF ORIGIN OF MUCOUS SUBSTANCES OF THE STOMACH

This table may help to prevent further misunderstanding in terminology and should obviate errors in interpretation of existent or further data on mucous substances of gastric origin.

#### SUMMARY AND CONCLUSIONS

1. The status of knowledge of mucous substances derived from the gastric secretion is critically reviewed.
2. Evidence is presented to show that the dissolved mucin of human gastric contents is not an entity but a mixture of at least two different viscous components which differ widely in many physical and chemical respects. De-

pending upon the mutual ratio of these components the physical and chemical properties of dissolved mucin will vary.

3. The principles of a procedure for separation and isolation of these two main components from the dissolved mucin complex of filtered human gastric juice are described. Some physical and chemical features of these two substances are listed. The two main components of dissolved mucin are named: dissolved gastric mucoprotein and dissolved gastric mucoproteose.

4. Dissolved gastric mucoprotein is very similar to, if not identical with, the compound isolated from canine gastric juice by Webster and Komarov as well as "gastro-globulin" isolated by Martin from human gastric juice.

5. Further evidence was found that dissolved mucoprotein is a product of mucoid chief cells of the gastric glands of the body and fundus.

6. Dissolved gastric mucoproteose contains a protein moiety showing the characteristics of a proteose as well as a viscous component related to mucopolysaccharides. The substance obtained by the same separation procedure from incubated, digested gastric mucus or from mucus after treatment with concentrated alkali shows almost identical characteristics to the dissolved mucoproteose obtained from filtered gastric juice.

7. There is evidence to show that dissolved mucoproteose of the filtered gastric juice is mainly derived from the digestion of the mucoid of the gastric surface epithelium mucus. Some additional evidence is introduced to show that the dissolved mucoproteose complex may also include a compound originating directly as a soluble product of the surface epithelium without passing through the stage of jelly-like mucus.

8. The presence of two quite different mucous substances, physically and chemically, in filtered human gastric juice strongly supports the dualistic theory of origin of mucous bodies in the stomach. Moreover, the evidence is submitted that dissolved mucoprotein has nothing to do with the secretion of the gastric surface epithelium.

9. A new classification of mucous substances derived from gastric secretion is presented. The site and mode of origin of these substances and their relation to clinical and physiological nomenclature of the visible gastric mucus and dissolved gastric mucin is discussed in broad lines.\*

\* References will be found at the conclusion of Part III.

# THE THREE MAIN COMPONENTS OF THE HUMAN GASTRIC MUCIN: DISSOLVED MUCOPROTEOSE, DISSOLVED MUCOPROTEIN, AND MUROID OF THE GASTRIC VISIBLE MUCUS

## PART II. METHOD FOR SEPARATION AND QUANTITATIVE DETERMINATION OF EACH MUOUS COMPONENT OF THE GASTRIC CONTENT

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### THE METHODS AVAILABLE FOR THE DETERMINATION OF GASTRIC MUCIN

The purely visual estimation of visible mucus in the gastric content, its volumetric determination by means of centrifugation,<sup>33, 34, 35</sup> or sedimentation,<sup>36</sup> obviously are not sufficient for scientific research. The hydration of the gel on which volume depends as well as the syneresis-imbibition equilibrium of the sol-gel structure of visible mucus depends upon the level of pH of the milieu and on crystalloid concentration in the mucus as well as in the secreted gastric juice. This is the reason why the volumetric determination of visible mucus in the gastric content proves misleading. Water, crystalloids and cells are only additive elements and are not the basis for the quantitative evaluation of the visible mucus content.

The same holds for the determination of dissolved mucin by approximate visual estimation of the viscosity of the filtered gastric juice<sup>37</sup> or by measurement of the speed of filtration<sup>38, 39</sup>. The viscosity depends not only on the dissolved components of gastric mucin but also on contamination with viscid constituents of the saliva and bile, on the acidity of the gastric juice and its relation to the isoelectric point of the viscous substances in the stomach. These methods should be discarded.

Methods developed on the principle that the dissolved mucin gives opacity with acetic<sup>40</sup> or trichloroacetic acid<sup>41</sup> the intensity of which corresponds to the mucin content of the gastric juice are also doomed to fail. Since the opacity developed by dissolved mucoprotein and dissolved mucoproteose in the same concentrations differ the result will depend, apart from contaminants, not only on the total content of gastric mucin but on the mutual ratio of these different substances in filtered gastric juice<sup>42</sup>. This is true also for the recently published method<sup>42</sup> which measures the opacity developing on addition of alcohol to the total filtrate of gastric juice after picric acid precipitation. The value of this method is further decreased by its standardization on sub-maxillary mucin, the opacity of which is very different from that of gastric mucin, and by the use of picric acid for precipitation which partly removes important products of mucus digestion.

Methods based on the quantitative determination of the polysaccharide moiety of gastric mucin would seem to be adequate and specific. This is, however, not the

case and the quantitative determination of reducing substances has so many pitfalls that it should, in our opinion be abandoned. In direct determination of reducing substances in native or filtered gastric juice<sup>43-47</sup> contamination with salivary mucin or food may falsify the data. Moreover, the determination without acid hydrolysis of the polysaccharide fraction gives only relative values and not a true picture of the amount of hydrolysable polysaccharides present. Determinations after acid hydrolysis (with<sup>44</sup> or without<sup>47</sup> deduction of the reducing values before hydrolysis) introduce other pitfalls. The results depend upon the length of hydrolysis, the concentration of the acid, and, above all, on the mutual ratio of the acid used for hydrolysis to the amount of polysaccharide substrate<sup>21, 48</sup>. The last cannot be predicted.

In addition, the determination of reducing substances in total mucin or total dissolved mucin depends not only on the concentration of the total mucin in the gastric content or fluid juice but also on the mutual ratio of various components of mucin, each of which has a different reducing substance content<sup>21</sup>. The same is true of the estimation of reducing substances in the total acetone precipitate of filtered gastric juice before<sup>43</sup> or after<sup>6</sup> hydrolysis. In both instances pitfalls are multiple: a) limitations of technic in respect to reducing substance determination; b) varying ratio of reducing power in various components of the dissolved mucin complex; c) contamination of the acetone precipitate of the gastric juice with co-precipitated saliva, bile and blood.

The estimation of the mucopolysaccharide fraction of mucin found its latest development in the method of Komarov, Siplet, and Shay<sup>23</sup> which employs the naphtho-resorcinol reaction in filtered gastric juice. In routine research it does not circumvent the interference of contaminants. Moreover objections have been raised to the use of the naphtho-resorcinol reaction<sup>49, 50</sup> in the presence of the proteins, amino acids and sugars found in gastric contents. This may explain why the mucin concentrations obtained with this method and compared with our iodometric method gave values which were 3-5 times higher<sup>51, 52</sup>. The valuable specific colorimetric reactions of sugars and glucuronic acid<sup>53, 54</sup> have been not yet adjusted to physiological or clinical routine.

The studies on gastric mucin by inadequate methods promote the appearance of conflicting reports. This is exemplified by the existing confusion on the influence of pilocarpine on gastric mucin, critically evaluated by Hollander<sup>55</sup>, the erroneous data on mucin deficit in peptic ulcer<sup>56-59</sup>, subsequently corrected by the iodometric method<sup>18, 60, 61</sup>, as well as misleading reports on lack of effect of insulin on mucin content of the human gastric juice<sup>42, 47</sup>, which are rectified in Part III of this paper.

#### IODOMETRIC AND TYROSINE METHODS

The main problems in mucin determination are adequate separation of mucin from contaminants and the fractionation of the total mucin into its components.

In the iodometric method, developed by one of us<sup>17</sup> the trichloroacetic acid precipitation removes pepsin as well as most mucous and protein contaminants

of the gastric content. On the other hand the dissolved gastric mucin remains in the filtrate\* from which it is quantitatively precipitated with one or one and one-half volumes of acetone at 40°C. This precipitate contains no dialysable products of protein disintegration<sup>18</sup>.

The iodometric method for the determination of the total dissolved mucin has been used by many workers<sup>51, 52, 60, 61, 67, 68, 69</sup> and found satisfactory, but it requires very accurate double titration and the standard is very difficult to reproduce. By substituting colorimetric determination of the tyrosine content of the dissolved mucin complex for the final determination of iodine-binding power we simplified the method and provided a better standard.

In the new tyrosine method<sup>19, 20</sup> we changed the final concentration of trichloroacetic acid from 8% to 3.3% to leave more proteose-like substances in the filtrate<sup>65</sup>. This explains why this method yields slightly higher values than the old. The dissolved mucin complex is precipitated with acetone from the trichloroacetic acid filtrate of filtered or centrifuged gastric juice. After alkaline hydrolysis its tyrosine content is colorimetrically determined by the Folin-Ciocalteu reaction<sup>70</sup> with the phenol reagent.

Since trichloroacetic acid precipitates most of the protein contaminants before mucin is precipitated and since the protein moiety of mucous components contains much tyrosine, the method seems adequate for routine mucin determinations. The determination on the basis of its protein (or peptid) moiety is safer than one based on the mucopolysaccharides of the total gastric juice for reasons discussed above. Moreover, the protein in the dissolved mucoprotein fraction of gastric mucin seems to play a role in the acid-base balance of the gastric contents and seems to be related in some way to the process of acid formation<sup>74</sup>. This is added reason for using the determination of the protein moiety of the mucous substances for the quantitative estimation of various fractions of gastric mucin. The tyrosine method was thoroughly compared with Kjeldahl values in the precipitates of dissolved mucin and good agreement of the results was obtained<sup>21</sup>.

The method, as previously published<sup>19, 20</sup> determined total dissolved mucin. Into it has now been incorporated the determination of the separate fractions of dissolved mucin<sup>21</sup>. The mucoprotein is separated by precipitation with acid from the alkaline solution of dissolved mucin complex at a pH about 2.0; this leaves the mucoproteose in solution. The calculations are adjusted to the average content of tyrosine in the isolated and dried fractions of mucoprotein (7.5%) and mucoproteose (3.9%).

\* The assertion that trichloroacetic acid precipitates gastric mucin<sup>42</sup> is erroneous and based upon studies with salivary mucin. In point of fact trichloroacetic acid precipitation of salivary mucin was included in our method to eliminate this contaminant without affecting gastric dissolved mucin. The trichloroacetic acid also precipitates the visible mucus of the gastric content. It does not precipitate the dissolved gastric mucoprotein<sup>5, 19, 21</sup> at room temperature in usual concentrations, and does not precipitate proteoses<sup>62-66</sup> or gastric mucoproteose<sup>21</sup>.



The quantitative determination of the mucoid of visible mucus has also been included although we do not attach much importance to this in clinical work. The amount of visible mucus collected does not reflect the amount of mucus secreted, much of which adheres to the gastric wall and is not recovered through the gastric tube. There is always the possibility of concomitant determination of the salivary mucus; this is precipitated by acid gastric juice and may be easily mistaken for the precipitate of gastric mucus. This danger is less in anacid gastric contents in which with some experience it is not difficult to differentiate the viscous components purely visually; this is described below. In experiments in which the salivary error may be avoided, quantitative determination of the visible mucus secretion in terms of its mucoid by the tyrosine method may be of importance.

Since the mucoid of the alkaline visible mucus precipitates on the addition of trichloroacetic acid, we have treated mucus first with alkali (in a final concentration of 1N). Then, this mucoid remains in solution after the subsequent addition of the adjusted amount of trichloroacetic acid.

The calculations were adjusted to the average tyrosine content of the mucoid of visible mucus, which is about 4.2 per cent, calculated as dry weight<sup>21</sup>.

METHOD FOR QUANTITATIVE DETERMINATION OF DISSOLVED  
MUCOPROTEOSE, DISSOLVED MUCOPROTEIN, AND MUCOID  
OF THE VISIBLE GASTRIC MUCUS

*The reagents and laboratory equipment necessary are:* 1. 10 per cent solution of trichloroacetic acid; 2. Acetone, U.S.P.; 3. 0.1 normal solution of sodium hydroxide; 4. 0.1 normal solution of hydrochloric acid; 5. 20 per cent solution of sodium hydroxide; 6. a 1:10,000 solution of L-tyrosine in 0.1 normal hydrochloric acid; 7. Folin-Ciocalteu phosphotungstic-phosphomolybdic phenol reagent\*; 8. a 23 per cent solution of trichloroacetic acid.

There should be available a Duboscq or photoelectric colorimeter, vacuum flasks for the filtration of highly contaminated gastric contents, graduated 15 and 30 cc. centrifuge tubes, and Pyrex tubes of 50 cc. volume with a mark at 25 cc. level.

*A. Separation of the visible mucus, fluid gastric juice, and contaminants  
from the gastric contents*

Recently collected gastric contents are left in labelled large test tubes for a short time and the supernatant foamy or purulent layers of mucus from the upper respiratory tract and saliva, if present, are removed by means of a small spoon. The remaining total gastric contents (without being shaken) are set

\* This may be made in the usual manner<sup>20, 20</sup> or purchased from Eimer and Amend Company, New York City.

into 15 or 30 cc. graduated tubes and centrifuged for 15–20 minutes at 3000 RPM until there is a distinct separation between the supernatant fluid and jelly-like material collecting at the bottom. If any material floats on the surface of the fluid it is again discarded with the spoon.

The relative volumes of total gastric contents ( $v_1$ ) and of total visible mucus fractions ( $v_2$ ) which have collected at the bottom of the centrifuge tubes are read on the graduations. All supernatant fluids are decanted into labelled test tubes and used for the determination of dissolved mucoproteose and dissolved mucoprotein as described under B, D and E or F.

The rest of residual fluids remaining above the mucus layers is discarded cautiously by means of a small pipette provided with a rubber bulb. The visible mucus fractions remain at the bottom of the tubes and their content in mucoid is determined as described under C, D, and E or F.

#### *B. Determination of the dissolved mucoproteose and dissolved mucoprotein*

The supernatant fluids from the centrifuged gastric contents, which are used for this determination, if not transparent should be filtered through regular rapid ( $\approx 1$ ) filters, using vacuum flasks to accelerate the filtration.

Four or five cc. of each fluid is transferred into a numbered test tube (10–12 cc. volume) by a volumetric pipette. To each sample of fluid one-half volume of 10 per cent trichloroacetic acid is added, i.e. one half cc. of acid for each one cc. of tested fluid. All samples are mixed by inverting them, left for about 10 minutes at room temperature in the rack and centrifuged for another 10 minutes at 3000 RPM. The supernatant fluids are decanted into small test tubes and 5 cc. of each fluid is transferred by pipettes into labelled centrifuge tubes of 15 cc. size.

One and one-half volumes of acetone i.e. 7.5 cc. are added to each tube. If only smaller amounts of gastric juice are available, the amounts of trichloroacetic acid and acetone should be adjusted, i.e. 1.5 cc. of acetone for each 1 cc. of gastric juice-trichloroacetic acid mixture. If the readings are done in a photo-electric colorimeter, only 3 cc. of the gastric juice-trichloroacetic acid mixture should be used from each sample, and 4.5 cc. of acetone added. The centrifuge tubes are closed by rubber stoppers, the contents are mixed by inverting them a few times and the tubes are set all together in an incubator at 40°C for one hour (or at 60° for 30–40 minutes) during which time the precipitate of dissolved mucin forms in the tubes. Afterwards the tubes are centrifuged at 3000 RPM for about 10 minutes, the supernatant clear fluids are poured off, and the few drops remaining on the walls and the edge of the tubes are quickly wiped off with filter paper or hygroscopic cotton, holding the tube in a slanting position. A compact precipitate containing mucoprotein and mucoproteose (total dissolved mucin) remains on the bottom of each tube.

To each mucin precipitate 2 cc. of 0.1 N sodium hydroxide are added and thin wooden applicators are used to stir them until they dissolve completely to form clear or slightly cloudy solutions without any floating particles. Three cc. of 0.1 N hydrochloric acid and 5 cc. of distilled water are added to each tube, which are now closed, inverted a few times for mixing and left standing in a rack for 20 minutes at room temperature. During this time mucoprotein precipitates in each tube as opal colored, extremely light and floating flocculi, which on stirring redissolve easily. If on addition of acid no flocculent opal colored precipitate develops after standing for 20 minutes at room temperature—very small amount or no mucoprotein is present. The turbidity of these fluids, if present, depends mainly on the mucoproteose turbidity in acid-salt milieu.

The tubes are carefully set in the centrifuge, avoiding any brisk movement which may cause redissolution of the mucoprotein precipitate, and are centrifuged for 10 minutes at 3000 RPM. The supernatant fluids containing dissolved mucoproteose fraction remaining in solution are decanted as completely as possible into Pyrex tubes, labelled "mucoproteose", having a mark at the 25 cc. level and numbered according to the number of the specimen from which they are derived.

The precipitates remaining after centrifugation contain mainly the mucoprotein, although they may include in some cases small amounts of contaminating mucoproteoses which have been salted out with the mucoprotein. Therefore it is advisable to redissolve the precipitate by addition of 2 cc. 0.1 N sodium hydroxide to each sample, using thin wooden applicators for stirring and then to add 3 cc. of 0.1 N hydrochloric acid again to each tube. The tubes are closed, inverted a few times for mixing and left standing again 20 minutes at room temperature in the rack. White opal-like floating mucoprotein flocculi again form in the tubes. The latter are carefully set in the centrifuge, and centrifuged for 10 minutes at 3000 RPM. The supernatant fluids, which contain the rest of the mucoproteose fraction are decanted as completely as possible and added to the Pyrex tubes containing respective mucoproteose solutions. The reprecipitation procedure described in this paragraph may be omitted, if the fraction precipitated with acid has the typical mucoprotein appearance.

The whitish precipitates remaining at the bottom of the centrifuge tubes contain now only precipitated mucoprotein; these are redissolved by adding to each tube 2 cc. of 0.1 N sodium hydroxide, using thin wooden applicators for stirring. The clear or slightly cloudy solutions of mucoprotein are now transferred to Pyrex tubes labelled "mucoprotein" and are numbered accordingly.

Any residue remaining at the bottom of each centrifuge tube is washed twice with 5 cc. of distilled water, which is added to its respective Pyrex tube, containing mucoprotein.

The determination is then continued as under D.

### *C. Determination of the mucoid of the visible gastric mucus*

In clinical research this whole paragraph (C) may be passed over.

To known volumes of visible mucus samples, separated as described under A, 20 per cent (5N) sodium hydroxide is added using one-fourth as much alkali as the volume of mucus, i.e. 0.25 cc. of 20 per cent sodium hydroxide for each 1 cc. of visible mucus. The tubes are closed with rubber stoppers and mixed thoroughly by inverting until complete liquefaction and homogenisation of the mixture occurs. Then, 23 per cent trichloroacetic acid is added to each tube in an amount equal to the sum of the volumes of both mucus and sodium hydroxide: for each 4 cc. of mucus, 1 cc. of sodium hydroxide and 5 cc. of trichloroacetic acid are added. (This brings the final concentration of free trichloroacetic acid in the mixture to 3.3 per cent; the rest is used to neutralize the excess of NaOH.)

The mixtures are left for 10 minutes at room temperature and filtered into test tubes through #2 filters. No vacuum flasks are required to accelerate this filtration. The turbid filtrates do not clear on further filtration.

If a Duboscq colorimeter is used for the readings, 3-5 cc. of each filtrate are transferred into 15 cc. centrifuge tubes and acetone is added to each tube in the ratio of 1.5 cc. of acetone for each 1 cc. of filtrate (i.e. from 4.5 to 7.5 cc. in this case). If the photoelectric colorimeter is used only 2 cc. of each filtrate and 3 cc. of acetone are used.

The tubes are closed with stoppers and the solutions are mixed by inverting a few times. The tubes are then set in an incubator for 1 hour at 40°C. During this time a heavy brownish precipitate forms; some of it falls to the bottom of the tubes, but some adheres to the walls at times forming a thin coating on the walls of the tubes. The particles of the precipitate which stick to the walls are carefully separated by rubbing with a thin glass rod so that they join the material collecting at the bottom. The tubes are then centrifuged for 5-10 minutes at 3000 RPM.

The supernatant fluids are discarded by decantation, the margins of the tubes are wiped with filter paper or cotton and 4 cc. of 0.1 N sodium hydroxide is added to each tube. The precipitates of the mucoid are stirred carefully with wooden applicators until all particles are dissolved and form cloudy solutions. The latter are transferred to Pyrex tubes labelled "mucoid", and numbered accordingly. The few drops remaining on the bottom of the centri-

fuge tubes are washed out using 5 cc. of distilled water twice. This water is added to respective Pyrex tubes.

The determination is then continued as under D.

#### D. *Alkaline hydrolysis of mucin solutions*

To each Pyrex tube containing mucoproteose, mucoprotein, or mucoid of the visible mucus, 1.5 cc. of 20 per cent (5N) sodium hydroxide is added. All tubes, each of which contains about 15 cc. of fluid, are placed simultaneously in a glass jar of about 2 liter capacity containing boiling water, and left therein for exactly 10 minutes; during this time the water should be kept boiling. Then the tubes are removed and cooled in water.

The procedure is then continued as described under E or F, depending upon which type of colorimeter is used.

#### E. *Colorimetric readings in Duboscq colorimeter and calculations*

The *standard solution of tyrosine* is prepared:

Into a Pyrex tube, marked at the 25 cc. level, 2 cc. of 1:10,000 solution of 1-tyrosine in 0.1N hydrochloric acid is slowly dropped out of a 2 cc. volumetric pipette. Then, in sequence are added in the tube 8 cc. of distilled water, 1.5 cc. of 20 per cent sodium hydroxide, again 8 cc. distilled water, 1.5 cc. of Folin-Ciocalteu phenol reagent, and finally again distilled water to bring the volume of the total mixture exactly to the 25 cc. mark. The tube is stoppered and the contents are mixed by inversion a few times and then left open.

To the first of the Pyrex tubes containing hydrolysed and cooled solutions of mucin fractions, 1.5 cc. of the Folin-Ciocalteu phenol reagent is added and the volume brought with distilled water exactly to the 25 cc. mark. The solution is mixed by inversion and is left open. The initial dirty green color of the solution will turn into a pure blue, the intensity of which depends upon the concentration of the mucous components. The same procedure is rapidly performed on all other tubes.

One should start readings not earlier than 10 and complete them not later than 30 minutes after the addition of the Folin-Ciocalteu reagent to the standard solution of tyrosine.

The colorimetric readings (y) are made in rapid succession in the usual way with the standard solution of tyrosine set at 20. If, however the blue color of the unknown is so pale that no determination can be made at this setting, the standard solution should be set at 10 and the calculations adjusted accordingly (compare Comment).

*Calculations* are made according to the corrected colorimetric formula for tyrosine determination<sup>19, 20</sup>:

$$(I) \quad \text{TE in mg.} = \frac{4.6}{y} - 0.03$$

in which "TE" (tyrosine equivalent) is the tyrosine content of the unknown mucin solution, and "y" is the reading of the unknown mucin solution taken with the standard solution containing 0.2 mg. of tyrosine set at 20.

Calculation of the *dissolved mucoproteose content*: To express the value per 100 cc. of centrifuged or filtered gastric juice the tyrosine value must be multiplied by  $\frac{150}{a}$  where "a" is the volume of gastric juice-trichloroacetic acid mixture used for acetone precipitation (1 cc. of gastric juice-trichloroacetic acid mixture corresponds to  $\frac{2}{3}$  cc. of native gastric juice).

The average tyrosine content of the mucoproteose is 3.9 per cent; the final formula for the calculation of the mucoproteose content in mg. per 100 cc. centrifuged or filtered gastric juice will be:  $\left(\frac{4.6}{y} - 0.03\right) \times \frac{150}{a} \times \frac{100}{3.9}$ , and after simplification:

$$(2) \text{ Mucoproteose in mg. per 100 cc. gastric juice} = \left(\frac{46}{y} - 0.3\right) \times \frac{385}{a}$$

where "y" and "a" are defined as above.

If "a" is 5 cc., as recommended for routine tests, the final simplified formula will be:

$$(2a) \text{ Mucoproteose in mg. per 100 cc. gastric juice} = \frac{3540}{y} - 23.$$

If the calculation of the mucoproteose concentration in total gastric content is preferred, the value obtained should be multiplied by  $\frac{v_1 - v_2}{v_1}$ , where "v<sub>1</sub>" is the total volume of the gastric contents and "v<sub>2</sub>" is the volume of visible mucus, determined as described under A.

Example: "y" = 17.7; "a" = 5 cc.; "v<sub>1</sub>" = 20 cc.; "v<sub>2</sub>" = 2 cc. Dissolved mucoproteose = 159 mg. per 100 cc. of total gastric content, and 177 mg. per 100 cc. of centrifuged fluid gastric juice.

Calculation of the *content of dissolved mucoprotein* is made in the same way, as in the case of mucoproteose but 7.5, the average content of tyrosine in mucoprotein, calculated per dry weight, is substituted for 3.9. The formula (3) is

$$(3) \text{ Mucoprotein in mg. per 100 cc gastric juice} = \left(\frac{46}{y} - 0.3\right) \times \frac{200}{a}$$

If "a" is 5 cc.:

$$(3a) \text{ Mucoprotein in mg. per 100 cc. gastric juice} = \frac{1840}{y} - 12$$

To convert this result into mucoproteose concentration per total gastric content, the value should be multiplied by  $\frac{v_1 - v_2}{v_1}$ .

The *content of the mucoid of the visible mucus* is calculated as follows: Since each 1 cc. of the mucus-alkali-trichloroacetic acid filtrate corresponds to 0.4 cc. of native visible mucus, the tyrosine content of each cc. will be:  $\left(\frac{4.6}{y} - 0.03\right) \times \frac{10}{4 \times a}$  where "y" is the reading of the unknown and "a" is the amount of mucus-alkali-trichloroacetic acid filtrate used for acetone precipitation. Since the tyrosine content of the mucoid of the visible mucus calculated as dry weight, averages 4.2 per cent, this value should be multiplied by  $\frac{100 \times 100}{4.2}$  for conversion into mg. of mucoid per 100 cc. of mucus. The final formula will be:

$$(4) \quad \text{Mucoid in mg. in 100 cc. of visible mucus} = \left(\frac{46}{y} - 0.3\right) \times \frac{595}{a}$$

For clinical purposes it is more important to determine the amount of the mucoid of the visible mucus per 100 cc. of total gastric content, since this value represents the amount of the mucin present in the gastric content in the form of the visible mucus fraction. To calculate this the formula (4) should be multiplied by  $\frac{v_2}{v_1}$ . The values "v<sub>1</sub>" and "v<sub>2</sub>" are determined as described under

A. The final formula will be:

$$(5) \quad \text{Mucoid of the visible mucus in mg. per 100 cc. of total gastric content} = \left(\frac{46}{y} - 0.3\right) \times \frac{595 \times v_2}{a \times v_1}$$

If, "a" = 5 cc., the formulas may be simplified as follows:

$$(4a) \quad \frac{5470}{y} - 36. \quad (5a) \quad \left(\frac{5470}{y} - 36\right) \times \frac{v_1}{v_2}$$

#### F. Readings in photoelectric colorimeter and calculations

If a photoelectric colorimeter is used the reading of the standard solution of tyrosine is established to obviate tyrosine standard readings at each series of determinations. The average value (R) is taken of several readings on the basis of several samples of the standard solution each containing 0.2 mg. tyrosine and using a red filter.

After "R" is established, to each of the tubes containing the hydrolysed and cooled solutions of mucin fractions, in rapid succession 1.5 cc. of Folin-Ciocalteu reagent is added, and the volumes are brought with distilled water exactly to the 25 cc. mark. The solutions are mixed by inversion and left standing open.

Starting not earlier than 10 and ending not later than 30 minutes after the addition of the Folin-Ciocalteu reagent to the first tube with mucin solution, photoelectric readings of the unknowns ( $r$ ) are made, bringing 5–10 cc. of each solution in rapid succession into the cell of the colorimeter and using the red filter.

*Calculations* are made according to the corrected colorimetric formula (1) for tyrosine determinations by the Folin-Ciocalteu reaction after its adjustment for readings in the photoelectric colorimeter:

$$(1b) \text{ TE in mg.} = \frac{0.23 \times r}{R} - 0.03. \text{ All equations described for use with}$$

the Duboscq colorimeter under E are adjusted here for use with the photoelectric colorimeter and numbered with the same number with the addition of the letter "b". The formulas will not be derived since the essentials were given under E.

$$(2b) \text{ Mucoproteose in mg. per 100 cc. gastric juice} = \left( \frac{2.3 \times r}{R} - 0.3 \right) \times \frac{385}{a}$$

$$(3b) \text{ Mucoprotein in mg. per 100 cc. gastric juice} = \left( \frac{2.3 \times r}{R} - 0.3 \right) \times \frac{200}{a}$$

For routine determinations these formulas should be simplified so that the photoelectric reading of the tyrosine standard "R" and the routine value "a" should be substituted in these equations. After performing a few simple algebraic functions these equations are greatly simplified.

Example: value "R" was found to be 400, and "a" used routinely for all determinations = 3 cc. The simplified equation (2b) will be: Mucoproteose =  $0.74 r - 38$ . If calculations of the mucoproteose and mucoprotein concentration per 100 cc. total gastric content are preferred, the values obtained should be multiplied by  $\frac{v_1 - v_2}{v_1}$  as described under A.

The calculations of the mucoid of the visible mucus are done as follows:

$$(4b) \text{ Mucoid in mg. per 100 cc. visible mucus} = \left( \frac{2.3 \times r}{R} - 0.3 \right) \times \frac{595}{a}$$

$$(5b) \text{ Mucoid of visible mucus in mg. per 100 cc. total gastric content} = \left( \frac{2.3 \times r}{R} - 0.3 \right) \times \frac{595 \times v_2}{a \times v_1}$$

These equations may be simplified in the same way as described above for equation (2b) of the mucoproteose.



## COMMENT

The mean error between duplicate and triplicate determinations has not exceeded 6 per cent if the method outlined is followed properly. If, however, the amount of material used for acetone precipitation (i.e. gastric juice-trichloroacetic acid mixture or mucus-alkali-trichloroacetic acid filtrate) is smaller than that recommended, the error will increase to 10–12 per cent.

The main source of error is not in the procedure but from changes which occur in the various mucous fractions from digestion on standing, as well as from large bile or blood contamination.

If these contaminants are not excessive, they can be removed by the procedures described so that the gastric juice-trichloroacetic acid mixture used for acetone precipitation is cloudy but no precipitate forms in it on standing. If very large, they cannot be removed by centrifugation, repeated filtration and trichloroacetic acid precipitation.

Some of the indefinite products of the enzymatic digestion of bile mucoid, or of food or blood proteins split products, are not precipitated by the trichloroacetic acid but are precipitated with acetone; therefore they can contaminate the acetone precipitate of the gastric dissolved mucin. On addition of acid they remain mostly in suspension with the mucoproteose fraction showing in the acid-salt milieu a highly turbid appearance. If this suspension is centrifuged, or left standing for a longer time, a compact, creamy-brownish deposit forms on the bottom of the tube; this, however, has nothing to do with the opal-colored, flocculent precipitate of the mucoprotein. As shown by their chemical and physical characteristics, these substances contain relatively small amounts of tyrosine and they are much less soluble in acid-salt solutions than the mucoproteose. It is obvious that the determination of the mucin fractions in these cases is not fully reliable, since the values obtained will be higher on account of the contaminating proteose-like substances. The values for mucoprotein will not be influenced by this contamination to a great extent, since this precipitate can be easily differentiated from the typical precipitate of the mucoprotein.

The cloudiness of the gastric-juice-trichloroacetic acid mixture after centrifugation or of the mucin-alkali-trichloroacetic acid filtrate depends on the turbidity of mucin solutions in acid milieu and its intensity depends on the content of mucous components in the material and their mutual ratio. It increases mainly with increase of mucoproteose or mucoid of the visible mucus.

It is very important to avoid changes in the mucous components on standing; these depend for the most part on dissolution and digestion of contaminating saliva and sputum as well as on the enzymatic digestion of some of the components of gastric mucin. Consequently it is absolutely necessary to remove the contaminants from gastric juice immediately after collection of a sample

and to use proper care in the early separation of the fluid gastric juice and visible mucus fraction in each specimen.

The fluid fraction separated from the visible mucus of gastric juice can be kept in the refrigerator for one day without appreciable change. However, it is much better to add trichloroacetic acid to the fluid gastric juice on the same day, centrifuge it, decant and keep this gastric juice-trichloroacetic acid mixture in the refrigerator. This material can be held safely for several days. Visible mucus can be kept in refrigeration only as the filtrate from the mucus-alkali-trichloroacetic acid mixture, or if added with  $\frac{1}{10}$  normal hydrochloric acid.

Saliva precipitated with gastric acid will contaminate the visible mucus fraction of the gastric contents and there is no safe way of discarding it, if once it enters. This is why, for clinical purposes, the quantitative determination of the mucoid of the visible mucus is unreliable in acid gastric contents. In the anacid gastric contents and with some experience gastric mucus can be easily differentiated from that of saliva by its darker color, extreme tenacity, homogeneous appearance and inclusion of gastric epithelial cells. If the material is obtained under gastroscopic control, there is less doubt as to the origin of the mucus. In such material the determination of the mucoid content, calculated in this case per 100 cc. of visible mucus, is more reliable and may have physiological or pharmacological significance.

Rarely with acid gastric contents, there may also be slight contamination of the dissolved mucoproteose fraction of the fluid gastric juice with digestion products of the swallowed salivary mucus. This is, however, negligible, since even on incubation for 6 hours, not more than 8 per cent of salivary mucus is digested and occurs in dissolved form. This value may be neglected in comparison to gastric mucoproteose concentration<sup>19, 25</sup>.

In some cases, using the Duboscq colorimeter, difficulties may arise in colorimetric matching of very weak and pale unknown solutions, if the standard is set at 20. In these cases the standard should be set at 10, the reading made, and the calculations adjusted accordingly. This is done by substituting the value 23 in place of 46 in the formulas 2, 3, 4 previously discussed.

A greenish tint of the solutions after addition of Folin reagent is due to the excessive acidity. This may be obviated by increasing slightly the amount of 20 per cent NaOH (to 1.8-2.0 cc) in both standard and unknown solutions.

A difficulty may arise with the photoelectric colorimeter in some very exceptional cases, in which the color of the unknown solution is too strong and exceeds the range of the photoelectric graduations. In this case no dilution of the intensively colored solution should be done. The Folin-Ciocalteu reaction does not correspond to the simple colorimetric formula and the result of a reading after dilution will be incorrect. In these exceptional cases a new determination must be made using only one-half of the original material (gastric

juice-trichloroacetic acid mixture or mucus-alkali-trichloroacetic acid mixture) so that all steps beginning with the acetone precipitation must be done again. This never occurs with the Duboscq colorimeter, the range of which allows measure of any concentration of mucin.

For clinical purposes the values of the mucoproteose and mucoprotein fractions should be calculated in mg. per 100 cc. of fluid gastric juice. The values of the mucoïd of the visible mucus, if obtained from the acid contents, should be calculated per total gastric content by means of formula (5), (5a), or (5b). If the determination is done on alkaline pure native mucus the calculation obviously should be done in mg. of mucoïd per 100 cc. of visible mucus by means of formula (4), (4a), or (4b). This value should be multiplied by the volume of mucus collected.

The transformation of the concentration values of components of mucin into total recovered values is done, as usual, by multiplication of the concentration per volume recovered in cc. and dividing by 100. Since the exact volumes of secretion in man are unknown, in routine studies for clinical purposes this data does not seem to have much value.

#### SUMMARY AND CONCLUSIONS

1. The available methods for the determination of gastric mucous substances are inadequate in view of the heterogeneity of gastric mucin. The obvious reasons for failures and confusion in the data on mucin secretion are discussed.

2. A routine method for separation and quantitative determination of three main components of the gastric mucin is described.

3. The method is based on: 1) separation of the fluid gastric juice and visible mucus; 2) removal of contaminants by means of trichloroacetic acid precipitation; 3) precipitation of the total dissolved mucin complex from the trichloroacetic acid filtrate with acetone at 40°C; 4) fractionation of the total dissolved mucin complex into dissolved mucoproteose and dissolved mucoprotein by dissolution of the mucin precipitate in dilute alkali and reprecipitation of the mucoprotein fraction from this solution with dilute HCl at a pH below 4; this leaves the mucoproteose fraction in solution; 5) dissolution of the visible mucus in alkali, precipitation of contaminants with trichloroacetic acid, and precipitation of the mucoïd of the visible mucus with acetone from the trichloroacetic acid filtrate; 6) quantitative estimation of each of the fractionated mucous substances on the basis of its tyrosine content after alkaline hydrolysis by means of the Folin-Ciocalteu colorimetric reaction with phosphotungstic-phosphomolybdic phenol reagent, using tyrosine solution as a standard.

4. The method is available for serial determinations of all gastric mucous components in several samples at once.\*

\* References will be found at the end of Part III.

# THE THREE MAIN COMPONENTS OF THE HUMAN GASTRIC MUCIN: DISSOLVED MUCOPROTEOSE, DISSOLVED MUCOPROTEIN, AND MUROID OF THE GASTRIC VISIBLE MUCUS

## PART III. PRELIMINARY DATA ON PHYSIOLOGICAL AND CLINICAL SIGNIFICANCE OF SEPARATE QUANTITATIVE DETERMINATION OF THE DISSOLVED MUCOPROTEOSE AND DISSOLVED MUCOPROTEIN IN THE GASTRIC JUICE OF MAN

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### INTRODUCTION

A search of the literature evaluating the physiological and clinical significance of gastric mucin is very disappointing because information is scanty and decidedly conflicting.

Wolf and Wolff<sup>51, 52</sup> studying the total mucin content of the human stomach by the iodometric method were unable to correlate mucin content of individual specimens with the titrable acid, the color of the membrane, its turgidity, stickiness, the presence or absence of bleeding, with the viscosity or specific gravity of the specimens, with the emotional status or life situation. Studies of the total mucin content in normal and ill individuals after histamine<sup>68</sup> or alcohol stimulation<sup>60</sup> did not reveal appreciable differences. On the other hand by determining the total mucous substances by the reducing power of gastric juice, Ihre<sup>47</sup> found some indication that high values of total dissolved mucin occur chiefly in duodenal ulcer and gastritis just as one of us (G. G.) found this independently by the iodometric method<sup>17</sup>. On the contrary Brummer<sup>42</sup> who employed his turbidity method found no clear difference between the mucin content of persons suffering from gastric disorders of any kind: "It is particularly to be noted that the mucin content of gastric juice of peptic ulcer and gastritis was normal."

These controversial or negative findings must be anticipated if no distinction is made between various fractions of mucous substances of gastric origin and if the total mucin content alone is determined. (See Parts I and II). Since each fraction of mucin has not only different chemical characteristics but also different physiological significance, the determination of the total mucin content cannot answer physiological and clinical questions connected with the mucin problem. The conditions are similar to those which would arise if any one interested in the finer mechanism of regulation of blood proteins would determine only the total protein content of the serum.

Kodejszko<sup>61</sup>, employing the iodometric method proved that some new information might be added by differentiating between the total mucin content of the gastric sample and its total dissolved mucin concentration. In fasting specimens he found low values of dissolved mucin in pernicious anemia and some cases of gastritis but no change in peptic ulcer, anacid gastritis, and gastric carcinoma. High values of the total mucin (mucus plus dissolved mucin) were found in peptic ulcer, hypertrophic gastritis and cancer of the stomach. These findings would suggest that under fasting conditions the secretion of visible mucus is increased in these diseases. After an alcohol test meal he found high values of dissolved mucin in duodenal ulcer, normoacid and hyperacid gastritis and total mucin values increased in these conditions as well as in hypoacid gastritis. This would seem to indicate that after alcohol stimulation there is an increased concentration of the dissolved mucin in duodenal ulcer and normoacid and hyperacid gastritis while in hypoacid gastritis there is an increase in visible mucus content. These studies represent the first fruitful endeavor to determine at least two components of gastric mucin simultaneously.

We are certain that much information of physiological and clinical importance can be gained from studies in which quantitative determination of all fractions of gastric mucin is done at once. The significance of fractionation of the mucin complex will be further elaborated in papers which follow; these will deal with the influence of insulin<sup>71</sup>, other vagotropic stimuli<sup>72</sup>, histamine and alcohol<sup>73</sup> on components of gastric mucin, the relation of secreted mucoprotein to the secretion of hydrochloric acid and the acid-base balance of the gastric juice<sup>74</sup>, mucin secretion in vagotomised and resected stomachs<sup>75</sup>, and the significance of the determination of dissolved mucoprotease for the "chemical diagnosis" of gastritis<sup>76</sup>. Some preliminary data will be presented in this paper for the purpose of illustration.

#### TOTAL DISSOLVED MUCIN AND ITS COMPONENTS IN FASTING GASTRIC CONTENTS

In Fig. 1, 170 determinations of the fasting total dissolved mucin concentration are plotted against the respective values of free acidity. The data were obtained from 100 normal persons and individuals with gastric lesions.

The concentrations of total dissolved mucin are spread over a large range in normal and pathologic material. Moreover, it is obvious that total dissolved mucin content of the fasting stomach shows no relation at all to the free acidity of the stomach. High and low total dissolved mucin values are found both in anacid and acid gastric contents.

In the acid fasting content, the free acidity of which was between 3 and 85 mEq per liter the range of values for total dissolved mucin was between 1.2

and 23.0 mg. TE (tyrosine equivalents) in 100 cc. of gastric juice with a mean value of 9.2 mg. TE in 94 determinations on 57 subjects. This value expressed in milligrams of total dissolved mucin corresponds to 184 mg. of total dissolved mucin in 100 cc. of gastric juice ( $\pm 24\%$ ).\*

In the anacid fasting gastric content, on the other hand, the range of the concentration of total dissolved mucin, based on 76 determinations in 57 individuals was spread even more and was between 1.6 and 47.1 mg. TE per 100 cc. gastric juice. Its mean value, however was very near the previous one and amounted to 10.4 mg. TE. If this value is expressed in dry weight of total dissolved mucin by multiplying with 20, it corresponds to 208 mg. total dissolved mucin per 100 cc. of gastric juice ( $\pm 24\%$ ). Furthermore, mean values of the dissolved mucin in the acid and anacid gastric content show close approximations; they are 180 and 184 mg. total dissolved mucin in 100 cc. gastric juice ( $\pm 24\%$ ) respectively.

On the basis of data plotted in Fig. 1, one might conclude that no relation whatsoever exists between the acid secretion and the dissolved mucin of the fasting stomach. This would be apparently justified by the finding of both high and low mucin values in both acid and anacid contents. This inference is entirely fallacious, as shown by Figure 2.

In Fig. 2 the concentrations of dissolved mucoproteose from 45 different gastric contents and mucoprotein from 51 different fasting contents are plotted against the respective free acidity values.

There is absolute evidence that the concentration of mucoproteose has no relation to the acidity of the gastric content. There is even a suggestion of the opposite relation (if any). The highest mucoproteose concentrations were found in anacid gastric contents and no suggestion of any proportional relation between the two values could be detected.

On the other hand there is a definite relation between the acidity of the stomach and its content of dissolved mucoprotein. Although the data are much too small as yet to determine whether the concentration of mucoprotein and the free acidity of the fasting gastric content are exactly proportional there is no doubt that in the anacid fasting content the mucoprotein is found only in

\* This value is calculated from the tyrosine equivalent (TE) which is multiplied by 20, for the tyrosine content of the total dissolved mucin averages 5.05%<sup>19</sup>.

After having isolated the two fractions from the dissolved mucin complex, it became evident that this multiplication factor must vary from case to case, depending upon the mutual ratio of mucoprotein and mucoproteose in total dissolved mucin complex. Since the tyrosine content of the dissolved mucoprotein is 7.5% and that of dissolved mucoproteose is only 3.9% we calculated that in the range of values of mucoprotein and mucoproteose in the fasting gastric content, the tyrosine concentration may vary between 4.0 and 6.2% instead of showing the fixed value of 5.0%. If, therefore the value of tyrosine equivalent is to be transformed into dry weight (on the basis of the average tyrosine content equalling 5%) with the multiplication factor of 20, the mean error in these calculations will be plus or minus 24%.

traces if at all, and that the high mucoprotein<sub>7</sub> values are found under fasting conditions only in patients showing<sub>2</sub> a hyperacid gastric content.

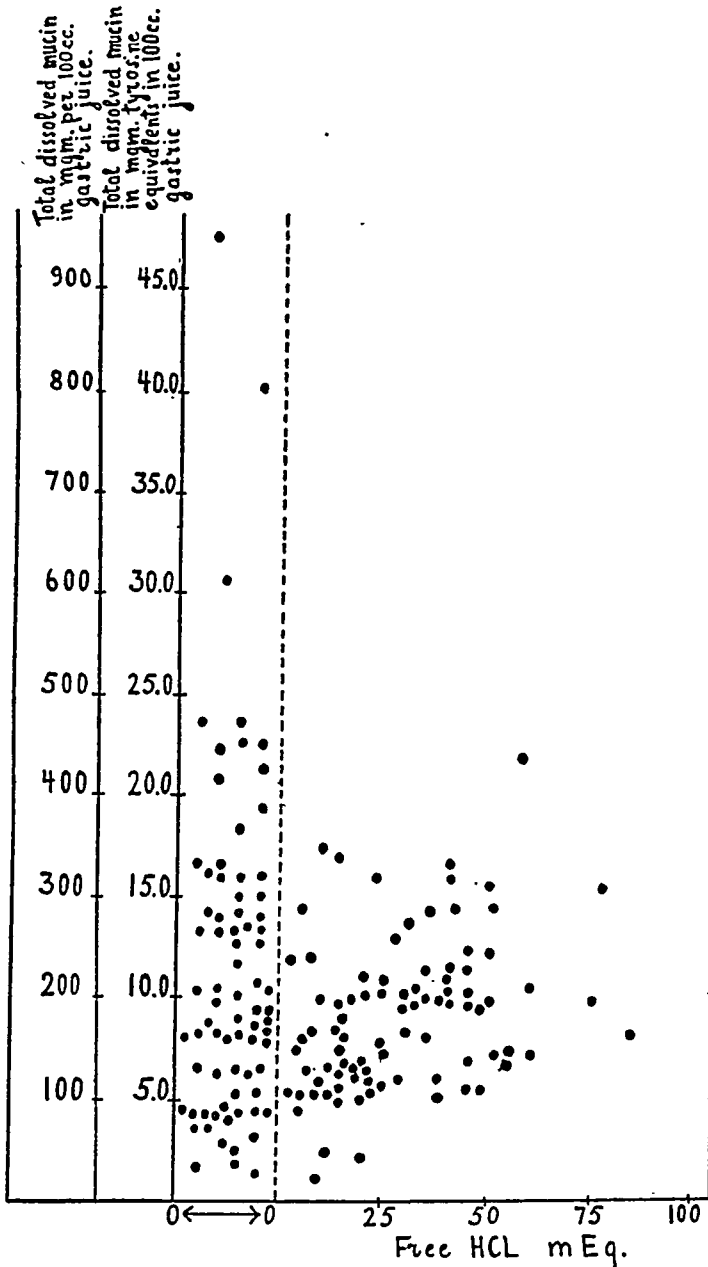


FIG. 1. Fasting total dissolved mucin and free HCL in 76 anacid and 94 acid gastric contents.

Further evidence of the value of the differentiation between mucin fractions is revealed by a comparison of the composition of the total dissolved mucin in anacid and acid fasting contents. This data, based on 48 determinations of the

dissolved mucoprotein and mucoproteose in the 24 anacid and 24 acid fasting gastric contents are shown in Fig. 3.

Each column of this figure represents one case; the total height of the column corresponds to the total dissolved mucin concentration; the shaded and unshaded areas show the amounts of mucoprotein and mucoproteose respectively in the dissolved mucin.

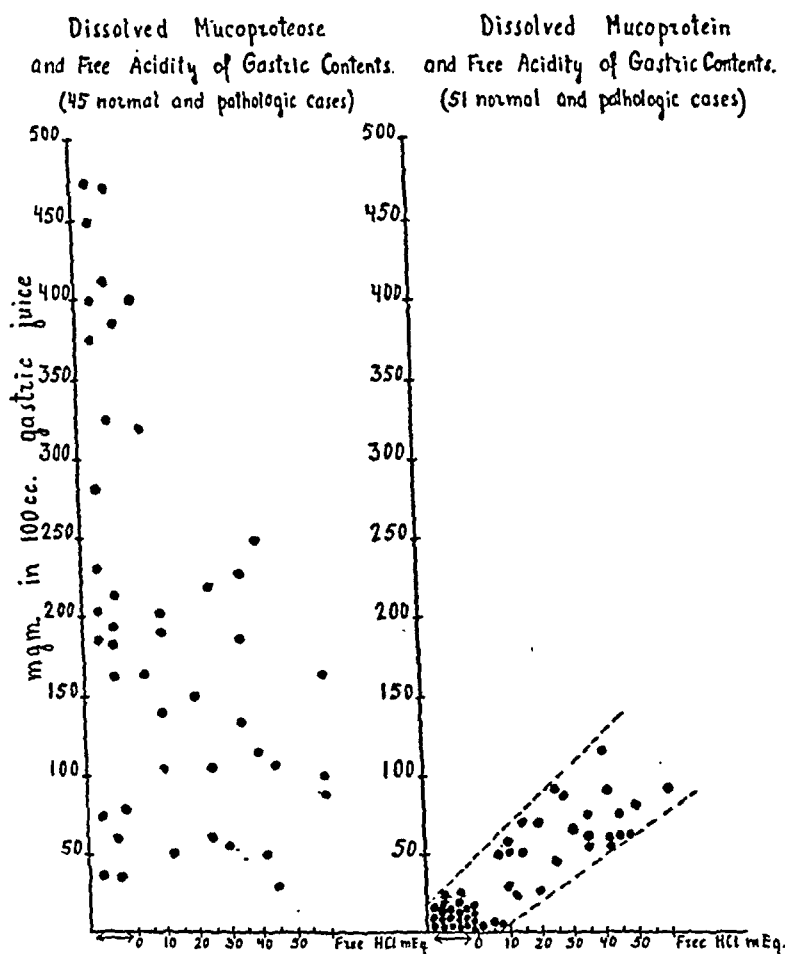


FIG. 2. Relation of the dissolved mucoproteose and dissolved mucoprotein concentrations to the free HCl of the fasting gastric contents.

A distinct difference is apparent from this figure in respect to the composition of the dissolved mucin in the anacid and acid gastric contents. In the anacid fasting content almost the entire dissolved mucin fraction consists of dissolved mucoproteose, the concentration of which in these subjects (pathologic cases were included) ranges between 39 and 703 mg., with an average value of 275 mg. of mucoproteose per 100 cc. of gastric juice.

The mucoprotein content in the anacid cases is, on the other hand, very small



and ranges between 0 and 26 milligrams with an average value of 14 mg. per 100 cc. of gastric juice. Since the ratio between mucoproteose and mucoprotein in anacid fasting gastric contents is about 20:1 on the average, it is safe to presume that the mucoprotein fraction of anacid fasting juice, if present at all, does not represent more than a small percentage of the total dissolved mucin content.

On the other hand it is evident from Fig. 3 that the mucoproteose content of acid fasting contents never attains values as high as in some cases of anacidity,

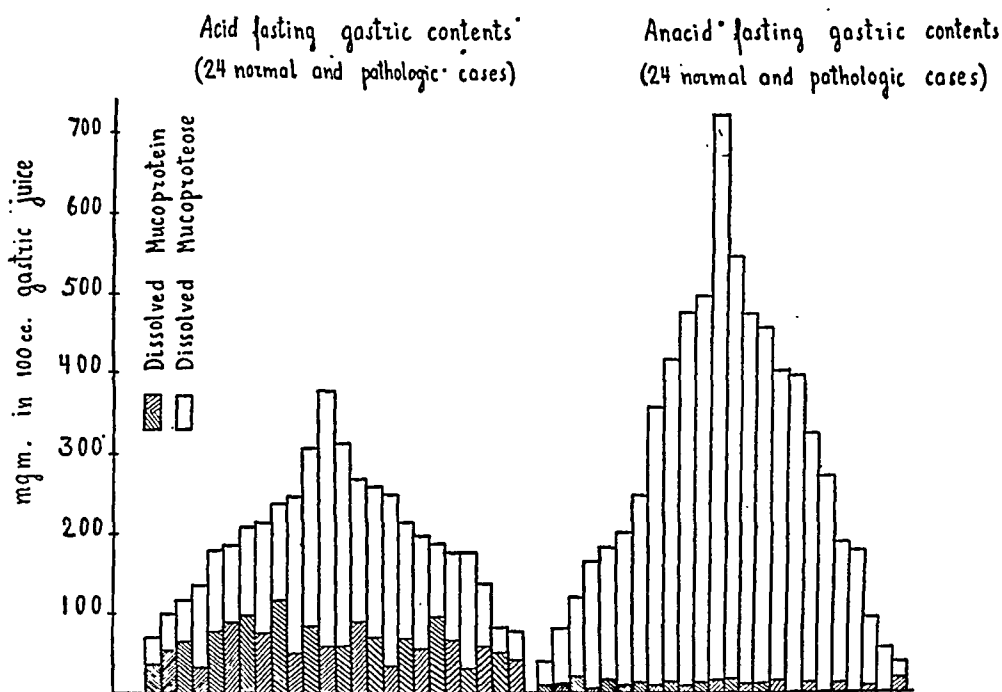


FIG. 3. Composition of the dissolved mucin in anacid and acid gastric contents. Respective amounts of dissolved mucoproteose and dissolved mucoprotein fractions in dissolved mucin specimens.

being in the range of 35 and 323 (average 134) mg. mucoproteose per 100 cc. of gastric juice.

Even more striking is the fact that the composition of total dissolved mucin of acid gastric content shows a relatively large amount of dissolved mucoprotein. The mucoprotein values in acid fasting gastric juice are between 30 and 117 mg. per 100 cc. of gastric juice. Owing to this fact and the relatively low level of mucoproteose in these cases, the share of mucoprotein in dissolved mucin of fasting acid gastric juice is fairly important and averages about  $\frac{1}{3}$  of the total dissolved mucin. The mean value of the ratio of mucoproteose to mucoprotein in anacid gastric juice was 20:1 but with acid contents it is 2.3:1.

The highest fasting mucoprotein value, which we have observed, was 167 mg. per 100 cc. gastric juice.

With these data it is possible to offer a new interpretation of some clinical findings concerning the fasting level of dissolved mucin in some pathological conditions. The upper and lower limits of the normal gastric content in total dissolved mucin are unknown owing to an inadequate number of perfect normals in our studies. It seems, however, that the upper limit of the fasting gastric contents in normals does not exceed 10.0 mg. TE, i.e. 200 mg. total dissolved mucin per 100 cc. gastric juice. Up to the present this upper limit of total dissolved mucin was exceeded in about 60 cases. The cases belonging to this group of exceptions included those with and without free hydrochloric acid.

We found increased levels of total dissolved mucin under fasting conditions in several groups of cases. Among them were: 1) irritable juvenile hyperacid or normoacid stomach; 2) duodenal ulcer; 3) hyper-, normo-, or anacid gastritis; 4) chronic alcoholism; 5) gastric retention due to pyloric stenosis; 6) after subtotal gastric resection; 7) after vagotomy.

The determination of both fractions of the dissolved mucin in these cases reveals that the increased level of total dissolved mucin in several of these groups has different meanings.

In anacid gastritis, in chronic alcoholism, with impaired gastric motility after vagotomy, sometimes after subtotal gastric resection, the increase of total dissolved mucin is due only to an increase of mucoproteose concentration. In view of the data presented in Part I, this increase would suggest an augmented formation of disintegration products of visible mucus, due either to increased activity of mucolytic enzymes or to an increased secretion of substrate for this enzymatic digestion i.e. gastric mucus from the surface epithelium. These findings harmonize with existing knowledge of the disturbed function of the surface epithelium cells in these cases. If gastroscopic studies now in progress<sup>76</sup> corroborate these findings, a "chemical diagnosis" of disturbed function of the surface epithelium as well as the diagnosis of gastritis should be possible by determination of the mucoproteose level. .

On the other hand in the hyperreactive irritable juvenile stomach with hyper- or normoacidity and in some cases of duodenal ulcer, the increase in total dissolved mucin level is due almost exclusively to the high value of mucoprotein with a normal level of mucoproteose. This is associated with high concentrations of the hydrochloric acid in the gastric content.

Finally in a group of cases including some duodenal ulcers, gastritis, and alcoholism with preserved gastric acidity, the increase under fasting conditions depends upon a rise in concentration of both fractions of dissolved mucin.

These preliminary findings outline a large field for clinical study on the dis-

solved mucoprotein and dissolved mucoproteose in various diseases of the stomach whereby some typical patterns of secretory mucin disturbances may be found in the future.

THE RELATION BETWEEN THE SECRETION OF DISSOLVED MUCOPROTEIN AND THE SECRETION OF HYDROCHLORIC ACID IN THE HUMAN STOMACH

The data supplied above make it probable that a relationship exists between the secretion of hydrochloric acid and of dissolved mucoprotein. Apparently whenever the secretion of hydrochloric acid begins or accelerates, the concentration of dissolved mucoprotein also increases in the gastric content. This is

TABLE 1

*Changes in the concentration of the dissolved mucoproteose and dissolved mucoprotein in fasting gastric specimens*

TEST	DISSOLVED MUCO- PROTEIN IN MG. PER 100 CC. GASTRIC JUICE		DISSOLVED MUCOPRO- TEOSE IN MG. PER 100 CC. GASTRIC JUICE		FREE AND TOTAL ACIDITY OF GASTRIC JUICE IN mEq.	
	Fasting specimens		Fasting specimens		Fasting specimens	
	1	2	1	2	1	2
1	6	50	120	50	0/8	14/20
2	10	64	205	52	0/10	30/40
3	0	95	230	115	0/10	20/33
4	0	75	180	137	0/10	35/48
5	5	25	197	160	0/10	12/20
Average value.....	4	62	186	103	0/10	22/32
Number of tests.....	5	5	5	5	5	5

indicated by data on the secretion of mucoprotein a) during spontaneous gastric secretion, b) after its stimulation by agents acting on the parietal cells (alcohol, histamine) and c) by vagal stimuli (insulin).

*Spontaneous secretion.* If the fasting gastric content is collected at intervals without withdrawing the tube and without other stimuli, it sometimes happens that the first specimen of the fasting content is anacid whereas the next contains free HCl. The acid in this case is secreted under the influence of local stimulation of the parietal cells by the tube or owing to psychic factors. Some examples relating to the secretion of mucoprotein under these conditions are listed in Table 1.

These figures indicate that with the beginning of secretion of HCl, mucoprotein simultaneously appears in the gastric content which did not contain it in appreciable amounts before the acid secretion started. At the same time the mucoproteose changes in the opposite direction and its concentration

decreases. This may be due to the dilution of gastric contents by the acid secretion.

*Stimulation of acid secretion by alcohol.* In more than 60 cases the mucous fractions of the gastric juice as well as its acidity were determined before and after alcohol test meal<sup>73</sup>. Ten examples showing the concentration of dissolved mucoprotein and mucoproteose before and after an alcohol test meal are listed in Table 2.

In this table the concentration of dissolved mucoprotein (1 hour after the alcohol meal) increases with increased acidity (Tests 1, 3, 5, 6, 10) or it remains

TABLE 2

*Changes in the concentration of the dissolved mucoprotein, dissolved mucoproteose, free and total acidity of the gastric juice after an alcohol test meal (100 cc. of 7 per cent alcohol)*

TEST	DISSOLVED MUCOPROTEIN IN MG. PER 100 CC. GASTRIC JUICE					DISSOLVED MUCOPROTEOSE IN MG. PER 100 CC. GASTRIC JUICE					FREE AND TOTAL ACIDITY OF THE GASTRIC JUICE IN mEq. PER LITER				
	Fast-ing	After alcohol				Fast-ing	After alcohol				Fast-ing	After alcohol			
		15'	30'	45'	60'		15'	30'	45'	60'		15'	30'	45'	60'
1	31	34	37	57	69	106	38	27	59	124	10/15	18/25	20/25	20/23	
2	70	26			53	190	85			99	12/30	4/10			16/25
3	23				44	77				46	5/12				25/40
4	90				81	96				75	60/75				40/62
5	5				87	184				80	0/10				30/60
6	10	40		97	70	205	27		80	47	0/18	40/45		62/75	60/75
7	13				12	80				42	0/10				0/10
8	6				52	230				150	0/10				0/10
9	5				18	190				58	0/10				0/10
10	13	16			27	541	183		61	309	0/10	6/12			9/22
Average . . . . .	27				51	200				103	9/20				20/33
No. of tests . . . . .	10				10	10				10	10				10

unchanged if acid secretion is not stimulated (Tests 2, 4, 7, 9). It may happen however that mucoprotein may be secreted after an alcohol meal even if no acid is formed (Test 8). On the other hand there is an almost constant and significant drop in the concentration of dissolved mucoproteose 1 hour after an alcohol test meal, in comparison to the fasting values.

*Stimulation of gastric secretion with histamine.* This confirms the data on the interrelation between the secretion of mucoprotein and of HCl. Ten histamine tests were performed on 10 normal subjects and those with gastric disease (Table 3). The concentration of dissolved mucoprotein, mucoproteose, free and total acidity of the gastric juice was determined before, 15, 30 and 60 minutes after the subcutaneous injection of 1 mg. of histamine. The fasting

values are mean data drawn from 2 or 3 fasting specimens collected at intervals of 15 minutes each.

In most cases (Table 3) 15 minutes after an injection of histamine, there is an increased concentration of dissolved mucoprotein in the gastric juice and this coincides with the beginning of the flow of HCl. Since the volume of the secretion also increases at the same time, the rise in mucoprotein concentration is due to an increased content of this substance in the specimen. The average increase approximates 50 per cent (from 46 up to 72 mg. on the average per 100 cc. gastric juice). This increase is, for the most part, of very short duration

TABLE 3

*Changes in the concentration of dissolved mucoprotein, dissolved mucoprotease, free and total acidity of the gastric juice after the injection of 1 mg. histamine*

TEST	DISSOLVED MUCOPROTEIN IN MG. PER 100 CC. GASTRIC JUICE				DISSOLVED MUCOPROTEOSE IN MG. PER 100 CC. GASTRIC JUICE				FREE AND TOTAL ACIDITY IN mEq. PER LITER			
	Fast-ing	After histamine			Fasting	After histamine			Fasting	After histamine		
		15'	30'	60'		15'	30'	60'		15'	30'	60'
1	75	89	53	45	137	102	103	45	35/48	80/92	97/105	100/110
2	5	53	45	12	35	63	59	124	0/5	63/73	79/90	62/73
3	10	69	30	20	165	70	69	80	30/38	70/98	30/40	10/20
4	5	20	12	5	150	135	141	140	0/10	50/68	52/72	32/55
5	64	73	10	50	52	68	121	47	30/40	88/100		80/90
6	52	65	55	45	49	36	27	55	42/55	75/93	90/115	85/105
7	95	151	129	117	115	162	106	97	20/32	30/37	55/68	42/51
8	94	111	47	10	95	85	72	124	60/77	82/105	93/120	90/100
9	7	9	14	11	186	142	95	95	0/6	7/20	10/25	21/32
10	55	77	65	48	112	104	57	49	32/50	50/70	68/90	75/95
Average.....	46	72	46	36	110	97	85	89	25/36	60/76	64/80	58/73

and lasts for another 15 minutes only in a minority of cases. Usually 30 minutes after the injection of histamine the mucoprotein level returns to its initial value. Forty to sixty minutes after the histamine stimulation, the concentration of dissolved mucoprotein falls below the initial fasting level.

In regard to the other component of dissolved mucin, the dissolved mucoprotease, usually it does not experience any increase of concentration after the injection of histamine although we observed two exceptions. Ordinarily for 15 minutes after the injection there is actually a steady drop in its concentration so that its level falls below the initial value. This trend of change in both components after histamine is shown in Fig. 4 which represents average curves drawn from 10 histamine tests.

If the influence of histamine on gastric mucin is studied by a method which does not allow the differentiation between the two fractions of dissolved gastric

mucin, the results and conclusions will be vastly different. The literature on gastric mucin reports that histamine does not stimulate the secretion of dissolved mucin in animals<sup>44, 22, 23, 24</sup> or in man<sup>47, 68, 42</sup>. Most authors found that the concentration of mucin even decreases after histamine<sup>44, 23</sup> in animals. In these studies the mucin was determined either as total dissolved mucin<sup>44, 23, 24</sup> or as total gastric mucin (including visible mucus)<sup>42</sup>. For the purpose of comparing the data obtained on separated mucoprotein and mucoproteose with those obtained on total dissolved gastric mucin, we performed 27 histamine

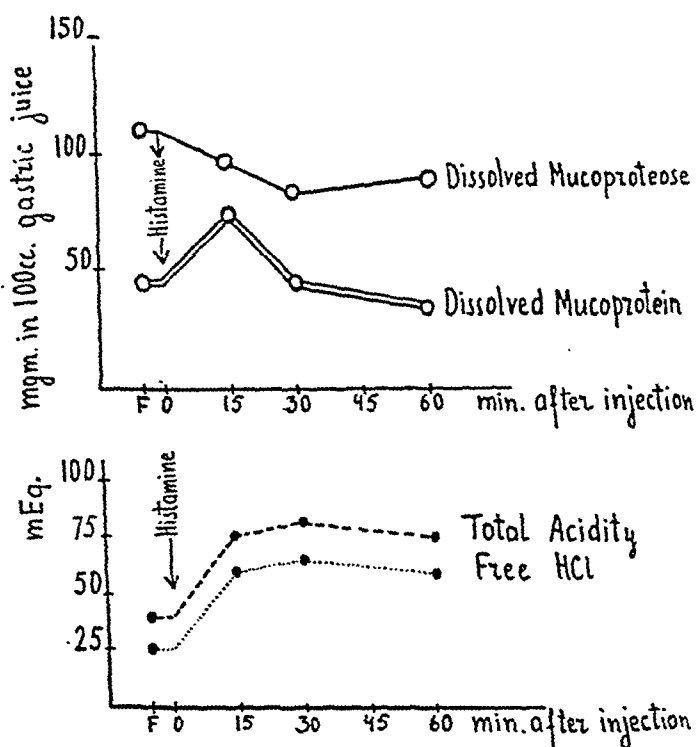


FIG. 4. Average curves of the dissolved mucoproteose, dissolved mucoprotein, and free HCl the gastric juice after histamine (1 mgm. subcutan.). Average of 10 tests.

tests on 25 subjects (normals and those with gastric pathology). In these tests we studied only the total dissolved mucin and the acidity of the gastric content before and after histamine without differentiating the two components of dissolved mucin. The data are listed in Table 4.

In one-half of the tests (Table 4) total dissolved mucin increased 15 minutes after the injection. In the other half, however, there was no increase or even a decline in concentration. If the average value is taken from the 27 experiments, the total dissolved mucin 15 minutes after histamine shows no change in comparison to the initial fasting value (181 mg. before histamine, 185 mg. 15 minutes after, on the average).

TABLE 4

*The effect of the subcutaneous injection of 1 mg. of histamine on the concentration of the total dissolved mucin and the free and total acidity of human gastric juice*

TEST	CASE	TOTAL DISSOLVE MUCIN CALCULATED IN MG.* PER 100 CC. OF GASTRIC JUICE					FREE AND TOTAL ACIDITY OF THE GASTRIC JUICE IN mEq. PER LITER					TOTAL VOLUME IN CC. OF THE GASTRIC JUICE RECOVERED				
		After histamine					Fasting	After histamine				Fasting	After histamine			
		15'	30'	45'	60'	75'		15'	30'	45'	60'		15'	30'	45'	60'
1	1	51	75	104	119		0/12	33/50	53/72	40/66						
2	2	124	152	186	115		0/8	10/18	22/30	16/24						
3	3	44	50	55	56		12/30	40/60	68/86	88/109	74/89	25	30	35	26	20
4	4	467	117	36	23		0/5	33/53		30/45	24/36	15	15		5	6
5	5	415	205	301	260		0/10	0/12	0/10	0/14		8	31	12	8	
6	6	116	178	154			0/10	38/65	50/70			15	16	8		
7	7	344	527	364			10/22	40/58	68/80			7	5	9		
8	8	125	114	76	96		0/8	42/57		35/50	20/35	30	22		20	21
9	9	197	140	95	95	116	34/48	98/125	124/132	108/118	106/116	45	50	62	48	40
10	10	120	153	128	112	110	0/5	30/55	55/73	80/95	40/55	8	30	34	15	14
11	11	141	170	127	140		22/40	70/85		90/100	82/92	20	41	30	31	
12	11	174	214	160			36/60	78/101		96/125		20	23		19	
13	12	111	116	156	97		44/62	39/50	88/100	76/94		86	55	70	35	
14	13	288	420	215	154	226	35/50	82/110	110/135	100/145	75/108	25	25	36	30	30
15	13	86	210	109	156	156	0/10	100/115		100/115	95/110	20	32		32	21
16	14	280	112	84	89	74	0/10	21/38	20/38	25/42		30	12	14	12	8
17	15	290	232	77			0/10	28/38	22/35			25	24	10		
18	16	245	233	128	111		60/77	82/105	93/120		90/100	28	38	29		26
19	17	143	158	100	93		30/38	70/98	30/40		10/20	10	50	12		11
20	18	228	354	276	252		20/32	30/37		55/68	42/51	47	29	30		35
21	19	220	214	166	131		35/48	80/92	97/105		100/110	16	23	30		61
22	20	156	124	95	84		0/6	7/20	10/25		21/32	13	11	15		16
23	21	27	129	113	115		0/5	63/73	79/90		62/73	23	29	35		39

24	22	116	128	104		111		42/55	75/93	90/111		85/105	60	50	52	40
25	23	120	109	114	108	116		0/10	50/68	52/72		32/55	8	20	18	15
26	24	126	163	109		113		30/40	88/100			80/90	10	10	7	12
27	25	135	190	136		104		32/50	50/70	68/90		75/95	30	35	25	30
Average.....		181	185	148	111	119		16/28	50/69	70/88	63/81	62/78	25	28	27	23
No. of tests.....		27	27	22	16	18		27	27	20	15	18	25	25	21	13

\* Plus or minus 24 per cent.



If the total dissolved mucin is studied at 15 minute intervals for an hour, the concentration of total dissolved mucin declines steadily in a majority of cases. The decrease averages about one-third of the initial value and is greatest 45–60 minutes after the injection. The average curve of total dissolved mucin, free and total acidity after histamine, drawn as a mean of 27 tests is shown in Fig. 5.

These figures confirm the finding that the total dissolved mucin content of human gastric juice, in general declines after histamine stimulation and that only in part of the cases is there a brief rise in the first 15 minutes after injection. This corresponds with the decrease noted in animal experimentation reported by Komarov et al<sup>22, 23, 24</sup> as well as with some clinical findings of Toby<sup>44</sup> who

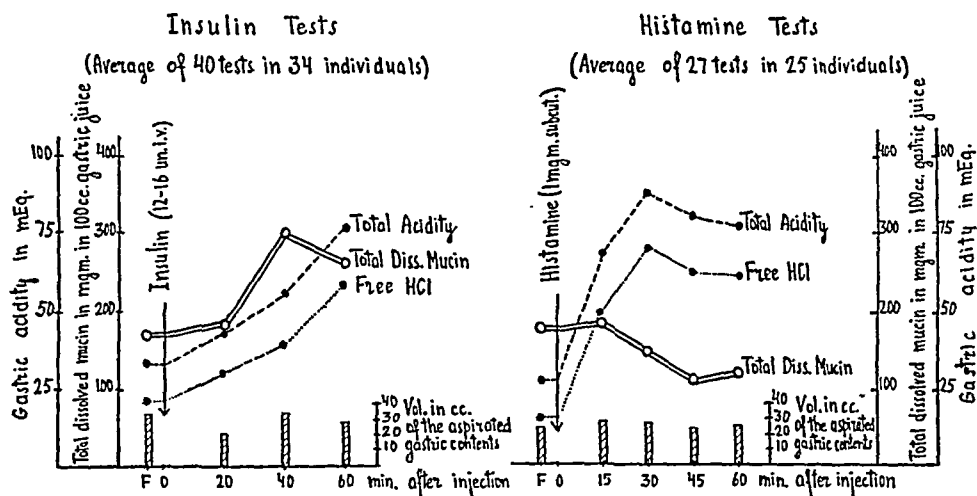


FIG. 5. Comparison of average curves of the total dissolved mucin and free and total acidity of the gastric juice after i.v. injection of 12–16 units insulin (average of 40 tests) and subcutaneous injection of 1 mgm. histamine (average of 27 tests).

found at times a short transient increase of reducing substances which she related to the increase of gastric mucin.

These results can, however, be further supplemented by a determination of separate fractions of dissolved mucin which were presented above. In the first 15 minutes after an injection of histamine there is an almost constant but not very pronounced increase in dissolved mucoprotein. This increase is manifested in some cases by the increase of total dissolved mucin (Tests 2, 7, 10 in Table 3). In a majority of cases however this increase is covered by a concomitant drop in the concentration of dissolved mucoproteose so that the total mucin content shows a decline.

In the further course of the histamine test there is a steady decline of both mucoprotein and mucoproteose.

In regard to the relation of the dissolved mucoprotein to the secretion of

HCl, the most interesting finding is the transient increase in mucoprotein observed for 15 minutes after an injection of histamine in man. Toby<sup>44</sup> made the same observation while measuring the total mucin content. In discussing the observations of Toby, Babkin<sup>4</sup> attributed them to "washing out" from the cells of preformed gastric mucin into the gastric lumen by the flow of acid gastric juice as the result of histamine stimulation.

Our data suggests that it is highly improbable that a "washing out phenomenon" satisfactorily explains the transient rise in mucoprotein after histamine for the increase in mucoprotein is selective and, in a vast majority of cases, is not accompanied by a simultaneous rise in the dissolved mucoprotease. If only a washing out process were involved, one would expect that the preformed product of surface epithelium would also be washed out by the flow of gastric juice. Actually, in our studies mucoprotease values decline, as a rule, at this time.

Babkin<sup>4</sup> also employed the "washing out" explanation to the transient increase of pepsin after histamine in man<sup>44</sup>. This explanation was supplemented by extensive studies by Osterberg, Vanzant, Alvarez and Rivers<sup>77, 78, 79</sup> who showed that histamine in man not only washes preformed pepsin out of the chief cells but a virtual increase in the secretory function of the chief cells also must occur under the influence of histamine.

It is almost certain from all available evidence that the secretion of the mucoïd cells of the gastric glands is dissolved mucoprotein, just as pepsin is the secretion of the chief cells of these glands. The influence of histamine on both, therefore, seems to be the same. Apparently there is not only washing out of preformed pepsin and mucoprotein from the chief and neck cells of the gastric glands but also a direct stimulation of the secretion of both of these substances in man after administration of histamine.

The histamine tests in respect to mucoprotein also corroborate the findings discussed above, namely, that *the secretion of mucoprotein is in some way related to the secretion of hydrochloric acid*.

This is not intended to state that this relation is based on the same secretory mechanism or that there is a strict parallelism between the secretion of mucoprotein and of hydrochloric acid. The influence of vagal stimulation with insulin on mucin and acid secretion which is discussed below, indicates that these substances show a different response to direct parietal and vagal stimuli. Stimulation of mucoprotein secretion by direct parietal cell stimuli causes a much poorer response than that observed after vagal stimulation; this is not the case with HCl which responds to humoral stimuli as well as to vagal stimuli.

Our evidence indicates that any flow of hydrochloric acid in the stomach, irrespective of its cause, results in a simultaneous appearance or increase in concentration of dissolved mucoprotein. Since the washing out phenomenon

alone does not explain the opposite behavior of the dissolved mucoproteose fraction, there must be a simultaneous transient increase in secretion of mucoprotein by its secretory organ. This finding may be related to the recent discovery of higher concentrations of total dissolved mucin in dogs at the beginning and towards the end of each secretory period of the stomach<sup>23</sup>.

This phenomenon may have a very important meaning. It is assumed that in the formation of hydrochloric acid an intermediary binding of chloride ions to a protein may be necessary to carry them into the lumen of the stomach. It is possible that the dissolved mucoprotein participates as an intermediary vehicle or buffer in the formation of HCl and its secretion in the stomach. There are several points which make this assumption plausible: a) both parietal and mucoïd cells are located in the same gastric glands; b) the great hydration of mucoprotein compound as precipitated from gastric juice makes it very probable that this is due to binding of some crystalloids by the peptide moiety of the mucoprotein; c) the crystalline structure of this substance may be an indication of this binding as happens in many other cases in human chemistry; d) the relatively large amount of protein moiety in mucoprotein makes the formation of acid albuminates possible; e) the constant surplus of chloride anions in respect to mineral bases available in gastric juice as found by us in studies with Dreker and Heisler<sup>74</sup> permits one to postulate a binding of part of the chlorides to proteins; f) the increase in this anion surplus after insulin stimulation parallels the increase in dissolved mucoprotein content of the stomach<sup>74</sup>. These facts suggest some binding which occurs between a part of the chloride ions and the dissolved mucoprotein.

The small content of mucoprotein in the gastric juice as well as the relatively small amount of chloride ions not bound to the mineral bases in fasting or insulin gastric juice<sup>74</sup> makes it improbable that much of HCl as formed is bound to mucoprotein. Nevertheless it is, in our opinion, very possible that some hydrochloric acid is secreted in the form of a compound in which it is bound to the protein group of dissolved mucoprotein. The short duration of the secretory phase of mucoprotein after humoral or vagal stimulation shows that the secretion of mucoprotein is exhausted very rapidly. When this occurs there is a considerable rise in acidity (Compare the curves in Fig. 5). This may indicate that with the exhaustion of mucoprotein secretion the buffering of HCl decreases and this manifests itself by a rise in free acidity. This problem will be discussed in detail in a subsequent report on acid-base balance of the gastric juice<sup>74</sup>.

#### THE EFFECT OF VAGAL STIMULATION WITH INSULIN ON THE DISSOLVED MUCOPROTEIN AND MUCOPROTEOSE OF THE HUMAN STOMACH

Stimulation of the vagus nerves or centers in the brain increases the gastric secretion of hydrochloric acid. These known facts were supplemented by

experimental studies of Oushakov<sup>80</sup> as well as by Babkin and his collaborators (Vineberg and Komarov<sup>33, 81</sup>, Baxter<sup>34</sup> Stavraky<sup>82</sup>), who showed that vagal stimulation also causes an increased secretion of pepsin and gastric mucus. This evidence was secured by experiments in which vagal stimulation was produced by an electric current, sham feeding, pilocarpine or mecholyl. It was, however, not clear whether the vagi influenced only surface epithelium cells or also mucoid cells of the gastric glands.

The data from Babkin's laboratory seemed not to concur with the data on gastric mucin in man since Ihre<sup>47</sup> and Brummer<sup>42</sup> found no evidence of increased mucin concentration after an intravenous injection of insulin; insulin is, as everyone knows, one of the most powerful vagal stimuli for gastric secretion.

In Table 5 our data on the influence of vagal stimulation with insulin on dissolved gastric mucin of the human stomach is submitted. These studies consisted of 40 tests on 34 individuals and the total dissolved mucin was determined by the tyrosine method<sup>20</sup> before, 20, 40, 60, and sometimes 90 minutes after an intravenous injection of 12–16 units of insulin.

The data (Table 5) show that the findings of Ihre and of Brummer depend upon an inadequate technic for mucin determination. We can amply confirm the thesis of Babkin<sup>4</sup> and his co-workers that vagal stimulation is a most important stimulus for the secretion of mucous substances of the stomach. In regard to man and to insulin stimulation we can supplement the findings of Vineberg, Komarov, Baxter, and Stavraky obtained on animals by other stimuli. Of 40 tests we find in 37 a great rise in concentration of the total dissolved mucin, usually 40 (but sometimes 60) minutes after an intravenous injection of insulin. This rise coincides with the peak of hypoglycemic symptoms in man and follows the fall in the blood sugar<sup>71</sup>.

The extent of increase in dissolved mucin after insulin is variable but it is almost constant. In some cases the initial fasting values were tripled, quadrupled or quintupled (Tests 13, 16, 20, 21, 23, 27, 28, 35). On the average the total dissolved mucin content increases from 172 to 300 mg. after 40 minutes. Statistically evaluated this rise is highly significant.

The increase in the dissolved mucin content coincides with the beginning of the acid secretion but the peak of mucin concentration in almost all our cases definitely precedes the peak of acid concentration; the latter develops about 20–40 minutes later when total mucin concentration starts to decline. These relations are shown in Figures 5 and 6. Fig. 5 shows a comparison of the effect of insulin and histamine on the concentration of total dissolved mucin in the gastric content as well as the free and total acidity. The insulin curve is an average of 40 tests and the histamine an average of 27 tests. It shows the superiority of vagal effect on the secretion of mucin as compared with histamine. Fig. 6 shows the average curves of total dissolved mucin, free and total acidity of the gastric juice obtained in eight tests (Nos. 1–8, Table 5) in which the

TABLE 5

*The effect of the intravenous injection of 12-16 units of insulin on the concentration of the total dissolved mucin and the free and total acidity of human gastric juice*

TEST	CASE	TOTAL DISSOLVED MUCIN CALCULATED IN MG.* PER 100 CC. GASTRIC JUICE					FREE AND TOTAL ACIDITY OF THE GASTRIC JUICE IN mEq. PER LITER					TOTAL VOLUME OF GASTRIC JUICE RECOVERED IN CC.				
		Fasting	After insulin				Fasting	After insulin				Fasting	After insulin			
			20'	40'	60'	90'		20'	40'	60'	90'		20'	40'	60'	90'
1	12	130	146	296	205	50/70	20/40	70/85	100/111	90/100	80	42	31	30	45	
2	10	104	99	251	220	15/25	20/30	20/36	36/65	40/70						
3	9	194	207	349	169	38/51	10/28	72/88	104/112	100/110	57	40	45	50	25	
4	13	126	316	328	196	43/75	65/110	25/152	125/145	105/125	42	20	31	60	15	
5	13	194	168	387	228	40/55	50/60	95/107	120/128	122/135	24	5	23	59	44	
6	26	211	343	495	442	50/65	60/75	45/62	70/85	70/85	29	10	40	35	44	
7	11	209	191	393	170	60/72	50/60	75/90	110/130	110/126	7	30	28	33	26	
8	8	222	226	300	290	0/5	26/34	20/32	25/45	25/40	19	10	11	12	4	
9	27	130	112	260	276	21/32	22/33	45/60	55/65		65	48	20	40		
10	27	136		112	276	20/40		16/34	50/104		36		33	30		
11	28	248		305	273	16/38		8/27	59/118		130		68	60		
12	28	244		330		12/32		13/30			42		82			
13	29	80	93	169	342	0/10	10/25	40/60	70/85		40	10	8	7		
14	32	335	260	534	365	0/10	12/22	22/40	52/68		30	10	19	20		
15	7	202		267		50/75			130/150		20			32		
16	14	82	135	364	†	0/10	0/12	5/30			40	20	44			
17	31	166	197	344	252	8/17	12/23	22/34	25/40		37	13	15	12		
18	15	77	98	140		22/35	60/70	27/35			70	7	14	6		
19	36	318	136	136	†	0/12		0/10			46		23			
20	16	111	131	382	212	—	68/87	85/92	98/105		26	26	40			
21	30	108	348	238	291	15/30	39/58	60/78	65/81		40	20	44			
22	30	140		286		16/34		68/91			25		22			
23	25	104	98	174	518	45/60	40/50	65/95	75/105		20	20	12			
24	40	214		330		40/65		48/77			61		64			
25	40	164		344		17/29		70/76			86		60			
26	21	115	117	272	216	62/73	26/40	55/70	70/82		39	17	42			

27	21	98	159	297	202		18/26	22/34 10/26	32/44 19/36 0/4	48/60 32/55		20	16	42	75
28	20	122	469	168			7/20					11		19	
29	42	220	376	376			0/6		72/107			18		20	
30	37	286	168	234			31/70		48/68			39		60	
31	39	98	168	454			38/59		10/26			36		12	
32	43	114	234	355			22/44		37/70			45		18	
33	44	324	454	355	†		20/44	0/12				12	6	10	21
34	46	398	200	234	232		0/10		27/53	76/110		54		16	
35	45	72	213	213	380		5/10		0/10	0/10		19		13	
36	33	193	256	296			0/10		18/36			16		20	
37	47	160	262	396	†		0/9		2/32						
38	48	102	262				0/10		0/10						
39	41	180	396				0/14		43/60			21		10	
40	49	166					36/55								
Average.....		172	182	300	281	213	21/33	30/45	39/56	59/77	83/99	33	19	31	32
No. of tests.....		40	20	39	22	8	39	21	38	27	8	36	19	34	28

\*  $\pm$  24 per cent.

† Only visible mucus.

determinations were made for a period of 90 minutes after the injection of insulin.

This average curve shows best the relation of the dissolved mucin to HCl secretion. It also shows that the rise in total dissolved mucin concentration represents a virtual increase in the total dissolved mucin content of the stomach since the volume of recovered gastric juice, as shown in this figure, does not undergo any decrease at the peak of mucin concentration.

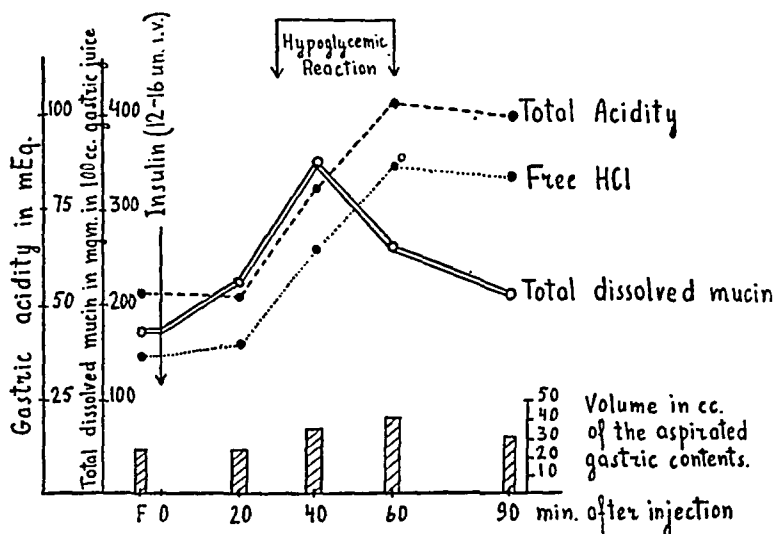


FIG. 6. Average curves of total dissolved mucin and free and total acidity of the gastric juice after i.v. injection of 12-16 units insulin (average of 8 tests).

It seemed important to ascertain which mucin component increased under vagal stimulation. In Table 6 is listed some of our data concerning the determination of dissolved mucoprotein and dissolved mucoproteose separately after intravenous injection of 12-16 units of insulin in 8 normal subjects as well as those with gastric pathology.

Table 6 shows that insulin stimulation causes, first of all, a great increase in the concentration of dissolved mucoprotein in the stomach. The mucoprotein concentration in all cases which we have studied up to now and in which a response in acidity was obtained after insulin, increases to values which, on the average, exceed fasting values 4 times (on the average from 35 under fasting conditions to 142 mg. per 100 cc. gastric juice 40 minutes after an injection of insulin). This increase is also statistically highly significant.

The peak of the increased mucoprotein occurs 40 minutes after the injection of insulin. It is synchronous with the peak of the hypoglycemic reaction. It precedes the peak of acidity by 20-40 minutes. Since there is no appreciable decrease in the volume of gastric juice at this time, the increase is due to augmented secretion.

Insulin stimulation also often causes an increase in the concentration of dissolved mucoproteose in human gastric juice. Since the fasting values of mucoproteose show a very wide spread, as stated above, it is difficult to state the average increase in mucoproteose after an injection of insulin. If we compare, however, the values of mucoproteose 20 minutes after insulin when no hypoglycemic symptoms occur and when there is no rise in mucoproteose with those at the peak of hypoglycemia (40–60 minutes after the injection), it is evident that the injection of insulin causes an increase in concentration in all cases listed in Table 6.

TABLE 6

*Changes in the concentration of dissolved mucoprotein, dissolved mucoproteose, free and total acidity of the gastric juice after the intravenous injection of 12–16 U. of insulin*

TEST	DISSOLVED MUCOPROTEIN IN MG. PER 100 CC. OF GASTRIC JUICE				DISSOLVED MUCOPROTEOSE IN MG. PER 100 CC. OF GASTRIC JUICE				FREE AND TOTAL ACIDITY IN mEq. PER LITER			
	Fast- ing	After insulin			Fast- ing	After insulin			Fasting	After insulin		
		20'	40'	60'		20'	40'	60'		20'	40'	60'
1	10	75	190	147	410	188	318	186	0/10	12/22	22/40	52/68
2	50	79	140	106	50	52	111	53	14/20	22/38	32/44	48/60
3	95	57	184	108	96	59	136	68	60/77	68/87	85/92	98/105
4	8	5	200	182	140	122	216	160	7/20	10/26	19/36	32/55
5	5	40	121	101	35	71	115	83	0/6	26/40	55/70	70/82
6	55	21	93	168	112	92	56	349	33/50	40/58	60/80	50/66
7	10	8	94	90	238	272	447	300	0/10	0/10	0/8	0/10
8	51	76	113	113	88	113	119	129	30/40	60/85	100/115	115/125
Average. . . .	35	45	142	128	146	121	190	165	18/28	28/46	47/60	58/71

The average curves of mucoprotein and of mucoproteose concentration in the gastric juice before and after insulin as drawn from 8 tests is shown in Fig. 7.

Further investigations are required to discover the cause of the increased concentration of mucoproteose after the intravenous injection of insulin. There might be increased secretion of the surface epithelium mucus<sup>80, 81</sup> which disintegrates rapidly under the enzymatic action. The increase in mucoproteose may also be due to augmented contractions of the stomach observed after insulin for this would mechanically press the preformed secretion out of the surface epithelium. Finally, under the influence of vagal stimulation a soluble mucoid-like substance may flow directly out from the surface epithelium (or from cardiac or pyloric glands as well). The rapidity with which the increase in mucoproteose occurs after an injection of insulin in some cases supports the last conjecture.

At all events, the results prove that the increase in total dissolved mucin after vagal stimulation by insulin in man mostly is due to increase in the muco-



protein. The rise in mucoproteose concentration after insulin is smaller and much more variable. Consequently we feel that the dissolved mucoprotein component is more appropriate for studies of the vagal influence on the stomach.

It also requires further investigations to determine what is the influence of the sympathetic nerve on the secretion of mucin fractions. The studies of Baxter<sup>34</sup>, Wolf and Wolff<sup>61</sup> and our data on the effect of ephedrin on the dis-

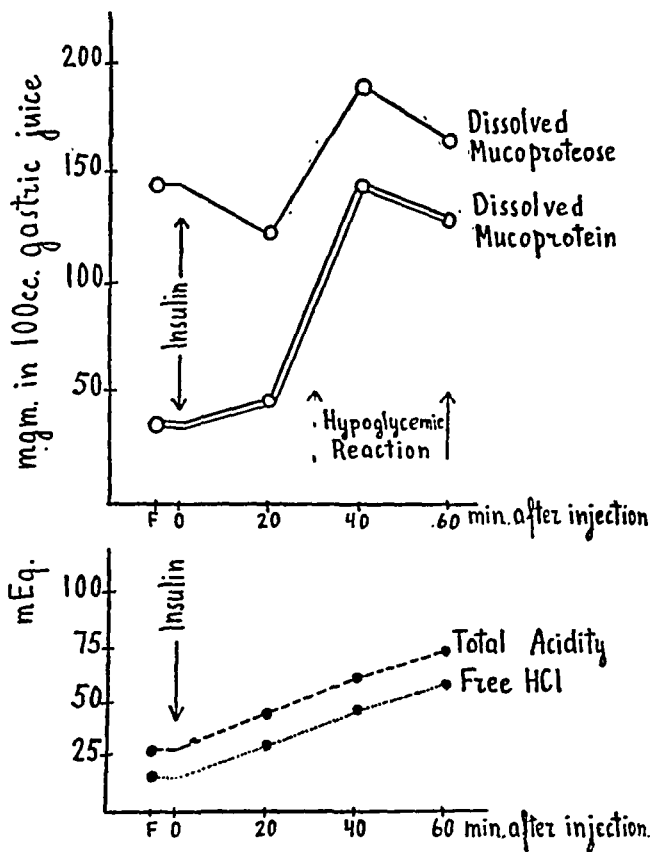


FIG. 7. Average curves of dissolved mucoproteose, dissolved mucoprotein and free and total acidity of the gastric juice after i.v. injection of 12-16 units insulin (average of 8 tests).

solved mucin concentration of the human gastric juice<sup>72</sup> seem to indicate that the sympathetic nerve influences to some extent the mucin secretion of the stomach. This effect, however, does not seem to be as constant and important as that of the vagus.

#### CONCENTRATION OF DISSOLVED MUCOPROTEIN AND MUCOPROTEOSE IN THE VAGOTOMISED AND RESECTED STOMACH

The role of the vagi in the stimulation of mucous secretion is shown by our data on the concentration of mucoprotein and mucoproteose in the human vagotomised stomach<sup>75</sup>.

Our preliminary data indicates that the human vagotomised stomach does not show any appreciable response in respect to the concentration of mucoprotein and mucoproteose in the gastric content after an intravenous injection of insulin. These findings can be correlated to the observations of Hollander et al, on animals<sup>83</sup> and on man<sup>84</sup>; he obtained a negative response of the acidity to insulin after complete section of the vagi.

The study of the dissolved mucoprotein after insulin stimulation in man may, therefore, be used for the evaluation of cutting the vagi in the same way as Hollander's test. It may even have some advantages in cases where vagotomy is combined with gastric resection. As pointed out by Paulson and Gladsden<sup>86</sup> and by Thorek<sup>85</sup> the negative response of acidity to insulin after vagotomy

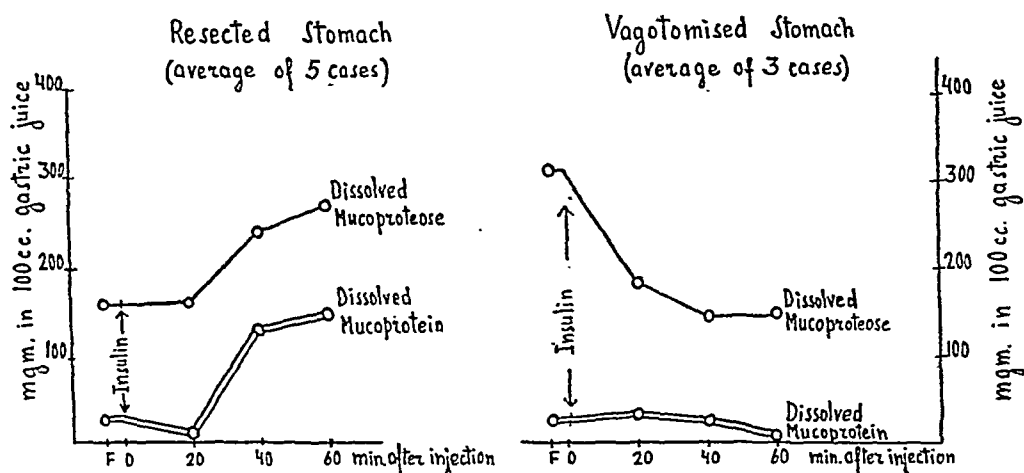


FIG. 8. Comparison of average curves of dissolved mucoprotein and dissolved mucoproteose of the gastric juice in resected and vagotomised stomach after i.v. injection of 12-16 units insulin.

associated with gastric resection or anastomosis, may depend upon the associated operation and not on the vagotomy itself for both vagotomy and resection would decrease the response of gastric acidity to insulin.

In such cases the study of gastric mucoprotein will give information which cannot be supplied by a simple study of acidity and indicate whether the vagi were completely or incompletely severed during operation.

Our preliminary data, obtained on 5 subjects with subtotal gastric resection has shown that an intravenous injection of insulin still produces a great increase in the concentration of dissolved mucoprotein and this is not less than that occurring after insulin injection in a patient with non-operated stomach. This finding might be expected since the mucoid cells of the gastric glands which secrete mucoprotein are located largely in the fundus and the body, the great part of which is preserved after subtotal gastric resection.

On the other hand, preliminary data obtained in three cases of trans-abdominal vagotomy with negative response of acidity to insulin, suggest that

TABLE 7

*Some physiological and clinical characteristics of the dissolved mucoprotein and dissolved mucoproteose of human gastric juice*

PHYSIOLOGICAL AND CLINICAL CHARACTERISTICS	DISSOLVED GASTRIC MUCOPROTEIN	DISSOLVED GASTRIC MUCOPROTEOSE
Place of origin in gastric mucosa:	Mucoid cells of the gastric glands	Columnar cells of the surface epithelium
Mechanism of origin:	Secretion	a) Enzymatic digestion of the visible surface epithelium mucus; b) probably also the secretion of a soluble (mucoproteose-like) form of the surface epithelium mucoid
Vagal mechanism of secretion:	Clearly evident but probably not exclusive	Evident but certainly not exclusive
Effect of vagal stimulation by insulin on the content of the substance in the gastric juice:	Marked increase in the content	Increase in content in some cases
Relation of the secretion of the substance to secretion of HCl:	Evident	None
Effect of histamine on the content of substance:	Initial increase for 15-30 minutes and then decline	Variable, but usually a steady decrease in the concentration
Effect of alcohol test meal on the content of substance:	Increase or no change depending upon the case	Decrease in most cases
Range of fasting values of normal subjects and those with gastric pathology:	0-167 mg. per 100 cc. gastric juice	35-703 mg. per 100 cc. gastric juice
Range of concentration of substance in gastric juice of normal subjects and those with gastric pathology, fasting and after vagal stimulation:	0-460 mg. per 100 cc. gastric juice	35-703 mg. per 100 cc. gastric juice
Gastric diseases or syndromes in which high values of the substance are found under fasting conditions or after alcohol test meal:	Some cases of hyperactive juvenile stomach, duodenal ulcer, hyperacid gastritis; pyloric stenosis due to ulcer, with hyperacidity	Some cases of anacid or hypoacid gastritis; chronic alcoholism; resected stomach; gastric retention due to pyloric stenosis or vagotomy; some gastro-duodenal ulcers
Effect of an injection of insulin on the concentration of substance in resected stomach:	Great increase in concentration similar to that in non-operated stomach	Increase in most cases
Effect of an injection of insulin on the concentration of the substance in the vagotomised stomach:	No or very small increase	No or very small increase

the completely vagotomised stomach does not respond or responds very little to an intravenous injection of insulin in respect to the dissolved mucoprotein.

Accordingly, if there is no or a low response of gastric acidity to insulin, but a definite increase in dissolved mucoprotein concentration, such as is observed in the nonoperated stomachs of Table 6, the negative Hollander test will not depend upon vagotomy itself but on the associated surgical procedure (resection or anastomosis). On the other hand, if there is no response in both acidity and mucoprotein to an intravenous injection of insulin, one may justly conclude that the vagi were cut completely.

These differences are shown in Fig. 8 which represents the average mucoprotein, mucoproteose, and acidity curves of 5 resected and 3 vagotomised stomachs.

We propose to publish in the future more extensive data on the applicability of this procedure for the evaluation of vagotomy in which the quantitation of the mucoprotein fraction will be greatly simplified for routine clinical use<sup>76, 71</sup>.

In Table 7 is listed a summary of the physiological and clinical data which we have collected up to the present on the mucoprotein and mucoproteose of gastric juice.

#### SUMMARY AND CONCLUSIONS

1. Evidence is advanced which suggests that the differentiation between two main fractions of dissolved gastric mucin of man possesses not only chemical importance but also definite physiological and clinical significance and implications.

2. Dissolved mucoproteose seems to be a product of surface epithelium and originates from the enzymatic digestion of the surface epithelium mucus. A part of this complex may also be derived directly from the surface epithelium cells as a soluble product, possibly to be secreted directly into the gastric lumen.

3. Dissolved mucoproteose is a constant component of gastric contents and its presence is not related directly to secretion of acid. The concentration in normal and abnormal subjects ranges between 35 and 700 mg. per 100 cc. of gastric juice.

4. The highest values of dissolved mucoproteose are found in anacid fasting fluid gastric contents and, for the most part, in patients having gastritis, chronic alcoholism or motility disturbances of the vagotomised stomach. Its concentration decreases regularly after alcohol or histamine stimulation of the stomach but usually increases following the intravenous injection of insulin. The significance of increased concentration of mucoproteose in the gastric contents for the purpose of a "chemical diagnosis" of gastritis is under investigation.

5. Dissolved mucoprotein, a second dissolved component of gastric mucin

seems to be a product of the mucoid cells of the gastric glands. Its concentration ranges between 0 and 460 mg. per 100 cc. of gastric juice.

6. The secretion of dissolved mucoprotein is related in some way to the secretion of hydrochloric acid. Any initiation or increase in the secretion of HCl is associated with an increased concentration of dissolved mucoprotein in the stomach. The increase in concentration usually is of very short duration and is rapidly exhausted.

7. The fasting gastric content of the juvenile, hyperacid, irritable stomach, of duodenal ulcer, and of some cases of hyper- or normoacid gastritis contains relatively high values of dissolved mucoprotein.

8. The possible role of dissolved mucoprotein as a buffer or a vehicle of hydrochloric acid is discussed.

9. Insulin represents the most constant and one of the most powerful stimuli for the secretion of dissolved mucoprotein, the concentration of which rises as much as four-fold with the appearance and the peak of the hypoglycemic reaction. The increase in the concentration of the gastric mucoproteose content of the stomach under the influence of insulin, is neither as constant nor as marked as that of mucoprotein.

10. The effect of insulin on dissolved mucoprotein and dissolved mucoproteose in man amply confirms the data of Babkin and his co-workers on the stimulating effect of the vagus on the mucus secretion in animals.

11. In the human vagotomised stomach the stimulating effect of an intravenous injection of insulin on the secretion of dissolved mucoprotein is abolished or greatly decreased.

12. In patients with a subtotally resected stomach the intravenous injection of insulin causes a rise in the concentration of mucoprotein and mucoproteose in the gastric content as distinct as that observed in the nonoperated stomach.

13. A test of the insulin effect on the concentration of the dissolved mucoprotein in the gastric content is suggested for the purpose of evaluating the section of the vagi after vagotomy. This test seems to be indicated particularly when vagotomy was associated with gastric resection and which yield a negative result with the Hollander test. An increase in mucoprotein and no response in acidity after insulin would indicate that the negative response of acidity was due to the resection and not to the vagotomy. The negative response of both acidity and of the dissolved mucoprotein content would indicate complete section of the vagi.

14. A test of the response of dissolved mucoprotein and mucoproteose to insulin stimulation may be used for the purpose of evaluating the functional activity of different mucous cells of the gastric mucosa. The response of mucoproteose should provide information on the activity of the surface epithelium cells and mucolytic enzymes; the response in mucoprotein should

indicate the activity of the mucoid cells of the gastric glands. This information may add new data to the gastric secretory tests which are employed in physiological and clinical research.

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## Case Reports

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### ACUTE CORROSIVE GASTRITIS: OBSERVATIONS ON THE GASTRIC MUCOSA FOLLOWING INGESTION OF CONCENTRATED HYDROCHLORIC ACID

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#### INTRODUCTION

Direct observation of the effect of ingested corrosive poisons on the gastric mucosa is important for both practical and research purposes, but the danger of the gastroscopic procedure following poisoning by strong agents usually precludes early and repeated studies. Late results are well known from roentgen investigations; gastroscopic information has necessarily been fragmentary.

Muñoz Monteavaro<sup>1</sup> has reported the earliest direct studies of the gastric mucosa following ingestion of corrosive substances. Three days after drinking bichloride of mercury, a patient at gastroscopy revealed mucosal congestion, hyperemia, and collections of mucus on the greater curvature and posterior wall of the proximal two-thirds of the stomach. Another patient who had swallowed arsenic seven days previously, showed hyperemia and edema of the proximal halves of the lesser and greater curvatures and the anterior wall; two months later chronic superficial gastritis was found, with areas of mucosal congestion and collections of mucus.

Ronchetti<sup>2</sup> gastroscoped a 17-year old girl 17 days after the ingestion of an unknown amount of caustic red, and found few changes other than generalized hyperemia; peristalsis was active, and the pylorus, although appearing a little small, opened and closed regularly. Henning<sup>3</sup> found hyperemia, edema, hemorrhages, and ulcerations following oxalic acid poisoning. Schindler<sup>4</sup> followed the case of a 19-year old girl who developed erosions, hyperemia and edema after hydrochloric acid poisoning, and eventually saw the return of a normal gastroscopic picture.

It appears from these few reports that corrosive poisons of various types have rather similar effects on the gastric mucosa. This is in contrast to the well-known rather characteristic quality of the surface changes produced by

many strong liquid agents on the stratified squamous epithelium of the buccal and esophageal mucosa—the necrosis of strong acids, the fixative action of mercuric bichloride, etc.

#### CASE REPORT

This 23-year old white male, previously well, began drinking heavily one evening, and, after consuming a liter of German wine, purchased a bottle of liquid from a passer-by. In a semi-stuporous state he drank two or three swallows from the bottle. The events from this point were not well recalled by the patient, but he remembered severe burning in the mouth and abdomen. After vomiting many times during the night, he sought hospitalization early the next morning. The suspicious bottle and its contents were recovered, and laboratory analysis revealed concentrated hydrochloric acid.

Upon admission examination, the patient was sluggish and apparently still inebriated to some extent. He vomited continuously, bringing up small amounts of dark brown material and fresh blood. There were necrotic ulcerations over the tongue and uvula. The epigastrium was exquisitely tender but there were no signs of peritoneal irritation and peristaltic sounds were heard. The admission WBC was 26,500 with 94% neutrophils.

Four hours after admission the temperature was 102°, and the course continued to be febrile for 48 hours in spite of large doses of penicillin. For five days the patient complained of severe epigastric pain and substernal fullness, and he vomited intermittently with continued loss of small amounts of blood. From this point there was gradual subjective improvement. He was able to retain a Sippy diet and inert antacids by the sixth day. The diet was advanced rapidly, until by the 40th day after the acid had been swallowed he was able to tolerate a full diet. The burns in the mouth healed by the 10th day, abdominal pain cleared by the 45th day, and substernal discomfort on swallowing by the 50th. Occult blood disappeared from the stools by the 51st. The patient was discharged from the hospital on the 57th day.

X-ray studies were first made on the seventh day. No abnormality was found other than spasticity of various segments of the stomach.

The first gastroscopic examination was made on the tenth day (Figure). The instrument was passed without difficulty and all parts of the stomach were well visualized. The interior configuration of the stomach was normal. The antrum and pylorus were normal anatomically, but no peristalsis was found. There was no spasm during the examination. There was severe mucosal damage, limited to the region of the cardia and the proximal half of the pars media. It was considerably more severe and extensive over the anterior wall than over the posterior. Only the most proximal part of the lesser curvature was affected, the changes fanning out over the walls from the cardia down towards the greater curvature of the pars media. The mucosal damage consisted of a severe hyperemic edema over the regions indicated, with obliteration of all rugae. The edema differed from that which is found gastroscopically in some cases of urticaria in that the surface here appeared rather

hard and dull, rather than succulent and fragile. There were two ulcerations on the anterior wall of the proximal pars media, each measuring an estimated two by two

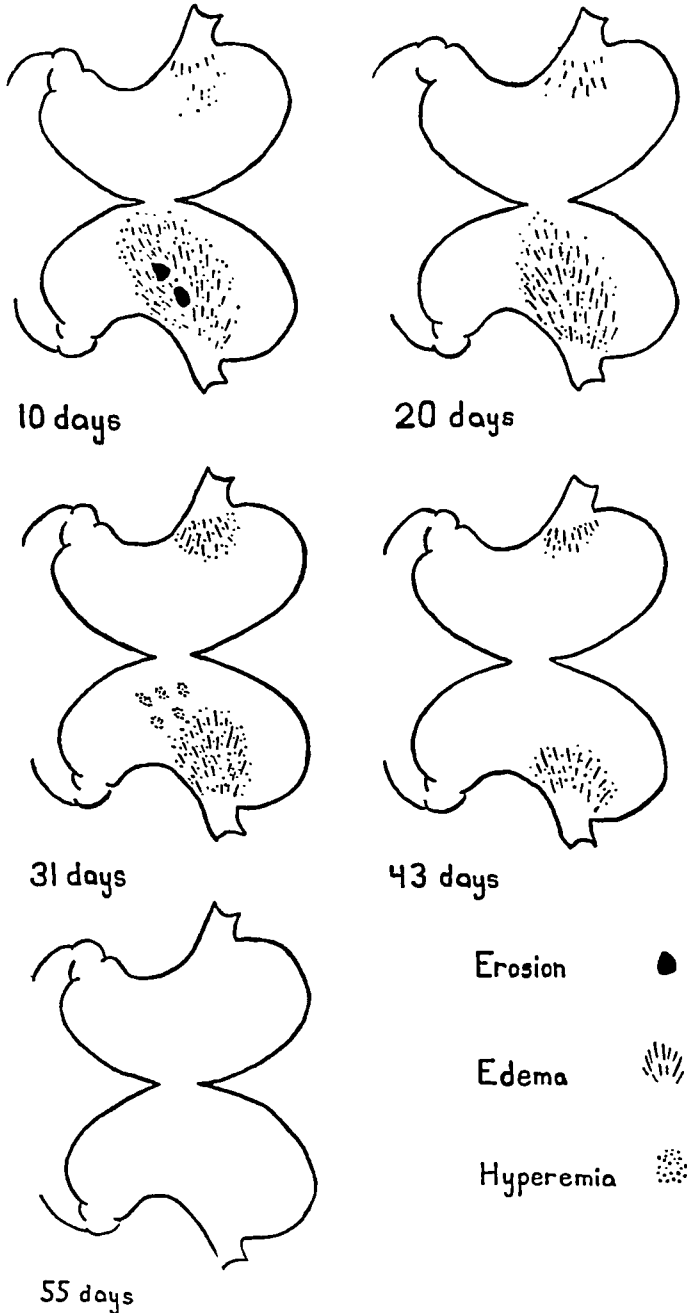


FIGURE. SCHEMATIC REPRESENTATION OF SERIAL GASTROSCOPIC FINDINGS

cm, and each with a dull green-brown necrotic base depressed perhaps a millimeter below the smooth swollen edges. There was no purulent exudate or unusual amount of mucus. There was a small amount of bleeding in the cardia, and the mucous lake was black.

The second gastroscopy on the 20th day showed that the ulcerated areas had healed over and that the mucosa was now everywhere intact. Otherwise, there had been little change in the picture. The distribution of the damage remained as before. The intensity of the hyperemia was striking. The edema was heavy enough to give the anterior wall a fixed appearance. There was no exudate and little mucus. No blood was found.

A gastric analysis with histamine on the 23rd day revealed no free acid and a maximum total acid of 3 CU.

X-ray studies on the 24th day showed no abnormality other than a hyperactive stomach.

On the 31st day, the third gastroscopic examination showed that the damage had begun to clear. The edema had receded on the anterior wall, leaving patches of simple hyperemia in the mid pars media. The mucosa about the cardia was still swollen, but at this time the edema appeared more succulent. There was no blood or exudate. Antral peristalsis was active and coordinated.

The next day gastric analysis with histamine elicited a maximum total acid of 26 and free acid of 16 CU.

On the 43rd day, gastroscopy revealed that improvement had been marked. There was now only mild edema and moderate hyperemia of the cardia. The pars media was normal. Antral and pyloric activity was normal. There was no exudate.

On the 55th day, the stomach was normal at gastroscopy.

#### DISCUSSION

Gray and Holmes<sup>5</sup> have emphasized that strong alkalis can be expected to cause extensive necrosis of the esophagus, with later cicatricial changes; however, since they are quickly neutralized in the stomach, they have relatively little effect here. On the other hand, strong acids usually affect the esophagus little as compared to the damage they cause in the stomach. As judged by the late effects, much of this damage is exerted on the pyloric region, for pyloric stenosis is a common sequela<sup>5, 6, 7, 8</sup>. In considering the cause for the stenosis which followed ingestion of sulfuric acid by a two year old baby, Vézina<sup>8</sup> concluded that immediate pyloric spasm had concentrated the acid in the pyloric region, with resulting maximum damage at that level. Schulenburg<sup>7</sup> had previously accepted this explanation for the stenosis which quickly followed the swallowing of hydrochloric acid by his patient, on the basis of the experimental radiologic evidence—gained by studies on dogs—presented by Testa<sup>9</sup>. This latter author had followed barium-caustic mixtures along the canine lesser curvature to the pre-antrum, where they caused spasm and delay and, subsequently, most severe damage at the point of delay. Degenhardt and Henderson<sup>6</sup>, too, have accepted this explanation. If the experimental evidence can be applied directly to the situation in man, and if, therefore, the clinical theory can be accepted, then rather satisfactory proof becomes available of the physiopathologic validity of the human Magenstrasse.

Gastroscopic information, however, does not lend support to this theory. In no case of corrosive poisoning studied gastroscopically and reported has predilection of the lesser curvature to mucosal damage been found. Rather, the changes have been diffuse over the proximal regions of the stomach, and, in most cases, the antrum and pylorus have been normal. No alternate theory to explain the late pyloric stenotic changes is offered at this time, but it is felt that it is necessary to consider not only the area of greatest concentration of the agent, but also the mere susceptibility of the antral region to noxious influences. Many histologic and clinical studies have indicated that the mucosa of the prepyloric region is "very much more sensitive than that of the corpus to those irritable agents to which the stomach is continually exposed. . ."<sup>10</sup>.

### CONCLUSIONS

As a result of several examinations one after the other in a case of corrosive gastritis and of a review of the brief literature on the subject, it is concluded that gastroscopic evidence points to an absence of any charactersitic gastric mucosal change resulting from the swallowing of various corrosive agents. The idea of a Magenstrasse is not supported by gastroscopic studies in cases of corrosive gastritis.

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## ACUTE PHLEGMONOUS GASTRITIS

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Acute phlegmonous gastritis is a rare condition apparently without consistent diagnostic findings. The persistent failure to diagnose this disease before operation or death indicates that progress may only be made in its recognition by collection of cases and evaluation of their diagnostic characteristics. Acute phlegmonous gastritis occupies a place in literature and textbooks yet is almost never mentioned among the more unusual conditions in a differential diagnosis.

### CASE REPORT

H. M., a 61 year old white male was admitted to the Veterans Administration Hospital, North Little Rock, Arkansas, on March 1, 1948, complaining of jaundice of about ten days duration. He was well until two weeks before admission. At that time he lost his appetite and had to force himself to eat. There was no pain nor discomfort of any type except anorexia. He continued working until five days before admission to the hospital. About ten days before admission his family told him that his eyes and skin looked yellow. For this reason he went to the Veterans Administration Regional Office where it was recommended that he come to the hospital.

About one year before admission he was discovered to have diabetes mellitus. This was regulated by ten units of protamine zinc insulin daily. About one month before admission there was a severe upper respiratory infection and this was thought responsible for his anorexia. In the six months preceding his entry into the hospital he had lost 24 pounds.

Physical examination on admission revealed a well developed, poorly nourished elderly white male. He appeared chronically ill and dehydrated. The skin and sclerae were markedly icteric. He was edentulous and the tongue was coated. The heart and lungs were within normal limits. The liver edge was 8 cm. below the costal border in the right midclavicular line and was not tender. The spleen was not palpable. Bilateral reducible inguinal herniae were present. The temperature was 98 degrees F., pulse 68 per minute, respirations 14 per minute, and blood pressure 112/62.

### ACCESSORY CLINICAL DATA

Exton Rose glucose tolerance test showed a fasting blood sugar of 151 mg.%,  $\frac{1}{2}$  hour 225 mg.%, 1 hour 254 mg.% with all urine specimens negative for sugar. Com-

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plete blood count and sedimentation rate were normal. Repeated urinalyses were positive for both bile and urobilinogen and occasionally for sugar. Cephalin flocculation test was 4 in 24 and 48 hours. Serum bilirubin ranged from 17.1 mg.% to 28.8 mg.%. Total protein was 6.80 gm. with 4.34 gm. of albumin. Alkaline phosphatase showed 4.8 Bodansky units. Prothrombin time was 61 seconds (control 52

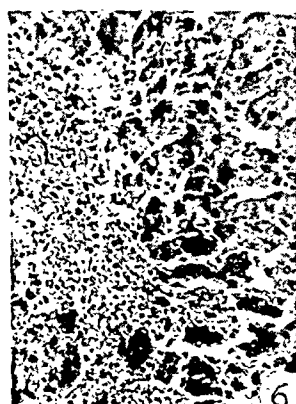


FIG. 1. GROSS VIEW OF STOMACH SHOWING SMOOTH MUCOSA ON LEFT AND THICKNESS OF WALL

FIG. 2. X-RAY OF STOMACH

The next film showed progression of the peristaltic wave and filling of the bulb. The apparent filling defect did not persist.

FIG. 3. THICKNESS OF STOMACH WALL WITH THROMBI IN SUB-MUCOSA

FIG. 4. MUCOSAL-SUBMUCOSAL JUNCTION OF STOMACH WITH MARKED LEUKOCYTIC INFILTRATION OF SUB-MUCOSA

FIG. 5. INFLAMMATORY INVOLVEMENT OF MUSCULARIS OF STOMACH

FIG. 6. AREA OF NECROSIS IN LIVER

seconds). Soft tissue x-rays of the upper right quadrant showed no evidence of stones in the gallbladder. Microfilm of the chest was negative. A needle liver biopsy on March 11, 1948, showed hepatitis with early cirrhosis. Gastrointestinal series (Fig. 2) was within normal limits.

#### COURSE

A preoperative diagnosis of carcinoma of the head of the pancreas was agreed upon. By this time, the jaundice had deepened. His anorexia had disappeared,



probably due to repeated small feedings. He had no pain or vomiting. The liver had decreased in size, was non-tender and no other masses were palpable. He remained afebrile during his entire 17-day preoperative period.

On March 18, 1948, the abdomen was explored. The anesthetic was nitrous oxide and oxygen with pentothal induction. The gallbladder was slightly enlarged. The stomach was found to be uniformly thickened, edematous and injected from the cardiac sphincter to the pylorus. The duodenum was explored and found to be highly mobile. The head of the pancreas was hard and surrounded by very firm lymph nodes. The common duct was visualized and thoroughly explored and there were no stones palpable in either the common or cystic ducts. The liver was deeply bile stained, yellow and had a finely granular surface. It was felt at the time of operation that this patient had a carcinoma of the head of the pancreas because of the presence of the firmness and the surrounding lymph node involvement. A palliative cholecystgastrostomy was done with great difficulty due to the boggy thick stomach wall. For the first two postoperative days the patient appeared to be progressing satisfactorily. Following this there was a spiking of the temperature which reached a maximum of 103 degrees F. on the third postoperative day. There was considerable hiccoughing and some respiratory difficulty. On March 22, 1948, the patient developed a grayish pallor and expired.

#### POST MORTEM EXAMINATION—GROSS OBSERVATIONS

Only the pertinent pathological changes are included in this report. The skin was golden yellow. A recent surgical incision was found in the right upper quadrant of the abdomen. There was 1200 cc. of a serous yellow-brown fluid in the peritoneal cavity, with some plastic yellow exudate along the lesser curvature of the stomach and around the tight cholecystgastrostomy. The stomach was dilated, with a generalized thickening of the wall (Fig. 1, 3) averaging 7 to 10 mm. in thickness. The muscularis and submucosa were obscured by moist, pale gray material. Most of the rugae had disappeared. The thickening of the wall stooped sharply both at the cardiac sphincter and at the pylorus. The stomach was dilated but contained very little fluid material. The fluid was yellow to gray, opaque, and slightly viscid. There was a moderate amount of edema of the wall of the duodenum and proximal jejunum. The liver weighed 1300 grams. The capsule was loose and the costal edge was unusually sharp. The liver parenchyma was yellowish-gray with patchy areas of softness. The anastomosis of the gallbladder to the stomach was tight. The common duct showed a very moderate dilatation; its mucosa was smooth and pale gray. The bile in the common duct was pale yellow gray and serous with a small amount of mucus. At the junction of the common and cystic ducts there was a large lymph node which was well circumscribed. The cut surface of this was soft, gray and friable. The pancreas weighed 110 grams and showed no abnormalities grossly. The pancreatic duct was not dilated.

#### MICROSCOPIC OBSERVATIONS

The stomach mucosa was of the usual thickness and generally showed the usual glandular pattern (Fig. 4). A few glands, however, were irregular in shape. Con-

gestion was marked in some areas of the mucosa. The submucosa showed a very heavy infiltration of leukocytes with marked edema and congestion throughout this layer (Fig. 4). The cellular infiltration appeared to terminate sharply at the junction of the mucosa with the submucosa. There was some edema and leukocytic infiltration of the muscularis and in several sections the polymorphonuclear leukocytic infiltration was seen to extend through the entire thickness of the wall to involve the serosa (Fig. 5). Some fibrin was deposited in strands on the serosa. In addition to the polymorphonuclear leukocytes in the serosa there was a moderate number of erythrocytes. No organisms were noted. Several of the vessels in the submucosa and muscularis showed the recent thrombi adherent to the vessel walls.

Sections of the liver showed congestion of the sinusoids. There was necrosis of the parenchymal cells, most particularly about the central veins but also near some of the portal spaces and beneath the capsule (Fig. 6). In these areas there was an infiltration of polymorphonuclear leukocytes and some mononuclear cells. The remainder of the parenchymal cells had swollen granular cytoplasm. There was fibrosis in the periportal areas and the portal spaces with an increased number of capillaries and proliferation of bile ducts. Sections of the heart showed minute areas of necrosis of the muscle fibers with patchy fibrosis in the myocardium. In the lungs there were large areas of atelectasis and congestion. There was mild interstitial fibrosis of the pancreas but no evidence of neoplastic change was seen. Sections from the lymph node located at the junction of the common and cystic ducts showed hyperplasia of the reticulo-endothelial cells with increased thickness of the trabeculae.

#### ANATOMICAL DIAGNOSIS

Acute phlegmonous gastritis, focal necroses of liver, jaundice, cholecystgastrostomy, fibrinous peritonitis, mucopurulent tracheo-bronchitis, pulmonary atelectasis. Portal hepatitis with beginning portal cirrhosis, ascites, emaciation. Coronary arteriosclerosis, myocardial fibrosis.

#### DISCUSSION

Acute phlegmonous gastritis is a relatively rare and frequently unrecognized condition. Although the disease has been known at least since the 17th Century<sup>1</sup>, only an occasional case has been recognized and diagnosed preoperatively. By 1919, 213 cases had been collected, yet a report on 1945 brings the total to less than 300 cases. The incidence in males is higher than in females. The condition occurs usually in the older age groups, although cases have been described in young adults.

Most reports are based on findings at surgery or upon post-mortem examination. The reason for this failure to make preoperative diagnoses appears to be because of the inconsistent symptomatology. Symptoms referable to the stomach as well as toxemia, and peritonitis with a fulminating course have been described<sup>2</sup>. Even in the event of proper preoperative diagnosis the prognosis

appears to be very poor. The case presented bears out the difficulties encountered in diagnosis and treatment. The only gastrointestinal symptom in this case was anorexia and the most prominent symptom was jaundice. The patient was not acutely ill at any time. Unfortunately, there was so little indication of gastrointestinal tract disease, preoperatively, that a gastric analysis was not done and no information is available as to the character of the stomach contents.

Both clinical studies and the post-mortem examination indicated liver damage. This was found to be of two varieties. The patient showed the findings of a portal cirrhosis by needle biopsy one week prior to operation. The post-mortem examination showed numerous focal necroses of the liver. It is not possible to state that the gastritis alone was entirely responsible for the liver changes.

The pathological changes of acute phlegmonous gastritis are predominantly in the submucosa but involve also the muscularis and the serosa. The picture may vary from an infiltration of polymorphonuclear leukocytes with considerable edema of tissue to the formation of pools of pus in the submucosa. A sharp demarcation of the process at the submucosa-mucosal junction is striking. The diffuse type is limited to the stomach with the process stopping sharply at the pylorus and the cardiac sphincter. Various authors have described this condition as associated with ulceration of the mucosa<sup>3, 4</sup>. These ulcerations have usually been associated with malignant neoplasms, or peptic ulcers of the stomach. Not all cases show mucosal ulceration or other direct routes for infection.

The etiology of this disease is as yet uncertain. In a large percentage of one series of cases streptococci were cultured from the stomach wall<sup>4</sup>. Other claimed etiological agents are direct contact with infected material in the stomach and septicemia<sup>3</sup>. The two most apparent routes of infection appear to be local extension through an ulcerated mucosa, and blood borne from a focus of infection elsewhere. Sachs and Angrist<sup>1</sup> believe the condition a manifestation of sepsis with localization in the stomach. In this case we were unable to demonstrate a loss of continuity of the stomach mucosa. The only known source of pre-existing infection was an upper respiratory infection described a short time previous to the onset of jaundice.

#### SUMMARY

1. A case of acute phlegmonous gastritis with symptoms directing attention to the liver is presented.
2. Post-mortem examination showed this case to be of the diffuse variety. No obvious portal of entry of infection was found in the stomach mucosa.

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# PERFORATION OF DUODENAL ULCER FOLLOWING VAGUS RESECTION

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Renewed interest in vagus resection for the treatment of peptic ulcer dates back to the report of Dragstedt<sup>1</sup> and his co-workers in 1943. Since that time reports concerning the clinical use of this procedure have been made by Grimson<sup>2</sup>, Moore<sup>3</sup>, and Walters<sup>4</sup>, with their associates. The most common complication following vagus resection has been gastric dilatation with delayed emptying time. Less frequent complications are diarrhea, abdominal distention and perforation.

The following case is reported because of the infrequency of perforation of a duodenal ulcer following vagus resection.

## CASE REPORT

B. R., a 53-year old white man, entered the St. Louis City Hospital on May 25, 1947, because of episodes of epigastric pain of four years duration. In 1943, a diagnosis of duodenal ulcer had been made at another hospital. He was placed on a bland diet and alkali. There was improvement, but the patient failed to adhere to the treatment for long periods of time. For the next three years there were bouts of abdominal pain that were controlled by diet and alkali. About one year before admission to the City Hospital the episodes of pain became more frequent and were not well controlled by the usual regime. He was treated in the out-patient clinic, but with only slight improvement. He was frequently awakened during the night by epigastric pain. This pain was relieved by food and alkali.

*Past Medical History:* Closure of perforated duodenal ulcer in 1943. Post-operative course was uneventful.

*Physical Examination:* Blood pressure 120/85; pulse 88/min.; respiration 16/min.; temperature 37° C. A well developed, fairly well nourished white man, who was not acutely ill.

*Abdomen:* Healed rectus wound in the right upper quadrant. Tenderness to palpation in the epigastrium.

*Laboratory data:* RBC 4.9 million; WBC 9,000; normal differential; Kahn negative; NPN 19; serum proteins—total 6.9 grams, albumin 4.74, globulin 2.16 grams, ratio 2.19.

*Gastrointestinal Series:* Revealed a persistent deformity of the duodenal bulb with retention of barium. After six hours there was approximately 20–30% residual of the barium in the stomach. Radiological diagnosis was duodenal ulcer.

*Gastric Analysis:* Fasting levels were 40 (mN) free acidity and 61 (mN) total acidity. Histamine 0.5 mg. was then injected subcutaneously. After thirty minutes

there was 74 (mN) free acidity and 85 (mN) total acidity. Results of the pre-operative insulin tolerance test are shown in figure 1.

A subdiaphragmatic vagus nerve resection was performed on May 31, 1947, according to the technique described by Crile<sup>5</sup>. The trunks of the right and the left vagus nerves were isolated and approximately three centimeters of each were removed. An anterior gastro-enterostomy was done. The anterior abdominal wall was closed with stainless steel wire. The postoperative course was uneventful. Microscopic sections of the tissue removed showed it to be nerve trunks. On the twelfth postoperative day the insulin tolerance test was repeated. (See figure 1.)

The patient was discharged from the hospital on the following day. About two weeks after discharge, the patient returned to his regular job as messenger at the

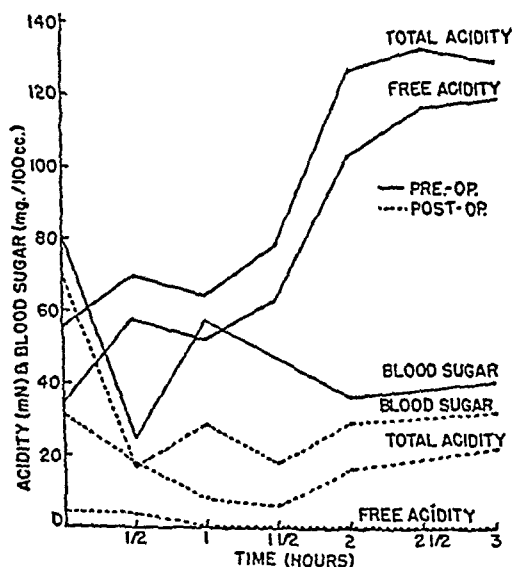


FIG. 1. ACIDITY AND INSULIN TOLERANCE TESTS BEFORE AND AFTER SUBDIAPHRAGMATIC VAGUS RESECTION FOR PEPTIC ULCER

hospital. He was completely free of pain and all foods were tolerated well. In fact, he stated that beer or whiskey did not cause him any abdominal discomfort. He gained several pounds in weight, and his general condition was much improved. In January of 1948, he was readmitted to the ENT Service because of sore throat of two weeks duration. Biopsy of the mass involving the epiglottis revealed squamous cell carcinoma, grade III. He was treated by external radiation. After the completion of the therapy, the patient returned to his routine duties. He showed considerable weight loss. There was marked regression of the lesion following x-ray therapy.

The patient was admitted to the hospital for the third time, at 7:30 p.m., September 14, 1948, because of severe abdominal pain. The night before admission the patient states that he drank about eight bottles of beer before going to bed. He felt well and had no complaints at that time. About five o'clock the following morning he was awakened by a severe pain in the epigastrium and the left upper quadrant. This pain caused him to double up and break out in a cold sweat. He drank a cup

of coffee and this made the pain more severe. This was followed by nausea and vomiting.

*Physical Examination:* Showed a well developed but poorly nourished 54-year old white man, who was lying doubled up in bed, and in acute pain. BP 146/44; pulse 100/min; temperature 38; respiration 20/min. Abdomen was of the scaphoid type. There was marked rigidity of the anterior abdominal wall, but it was most spastic in the left upper quadrant. There was rebound tenderness in all quadrants. There was absence of bowel sounds. Rectal examination caused moderate discomfort. Radiological examination of the lower thorax and upper abdomen in the upright position, and of the abdomen in the right lateral decubitus position, revealed considerable amounts of free air under the diaphragm, indicating the presence of a ruptured viscus.

*Laboratory data on admission:* RBC 5.4 million; WBC 13,500; Hb 14.5 Grams. The differential count showed a definite left shift.

Exploration of the abdomen was performed shortly after admission. A perforation that measured about 5.0 millimeters in diameter was found in the anterior wall of the duodenum about 3.5 centimeters distal to the pylorus. The perforation was closed and covered with an omental graft. The cardia and esophageal regions were explored, but the vagus nerve trunks were not found. The gastrojejunal stoma was adequate and patent. The anterior abdominal wall was closed in layers. The postoperative course was uneventful. The insulin tolerance test was repeated on the fourteenth day following operation. The results were very similar to the postoperative test shown in figure 1. The patient was discharged from the hospital on September 29, 1948. He was examined four weeks later in the out-patient clinic, and his condition was satisfactory.

Clinically, this patient was much improved by vagus resection, because the epigastric pain was abolished and all foods were tolerated well. Despite this clinical improvement, there was an acute perforation of an ulcer involving the anterior duodenal wall fifteen and one-half months following operation.

#### SUMMARY

A case is reported in which there was a recurrence of a duodenal ulcer with perforation following a vagus nerve resection and anterior gastrojejunostomy. The operation appeared to be adequate by the response to the insulin test.

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### CALORIC VERSUS PROTEIN NEEDS DURING DIETARY RESTRICTION

A restriction in the normal intake of food is sometimes necessary or advisable. Three examples may be cited: (1) Soldiers, sailors and marines (or others) detached from their normal food supply for one reason or another. In such cases a limited supply of food is advisable so that in the smallest bulk prolongation of life for the greatest period with the least physiological impairment will be possible. A great deal of investigative work has been and is even now being carried out by the armed services dealing with this problem. (2) Patients who are so ill that they are literally unable to eat all of the normal diet. Serious nutritional deficiencies can be avoided in such cases at least for short periods of time if a specially devised restricted diet is provided, i.e., one which provokes little or no physiological impairment. (3) Patients who for one reason or another are unable to take anything by mouth and in whom one must therefore resort to parenteral feeding in order to avoid the effects of starvation. Here, too, it is advisable to inject only as much solution together with the essential food elements as is absolutely necessary so as to reduce to a minimum the expense and inconvenience, and potential danger inevitably connected with this method of alimentation.

Any restriction in the normal food requirements obviously means wastage of body tissue. Now the body tissues consumed during starvation (aside from water, salt and vitamins) are largely the protein and the adipose depots. Most authorities now agree that the depletion of protein leads to physiological impairment whereas adipose tissue can be consumed ordinarily without harm and is thus generally classed as a true source of dispensable body food. *A priori* one would say, therefore, that some restriction in the caloric requirements would be justified as long as adipose tissue is available for this purpose. This is fortunate because energy needs comprise up to 80 per cent or more of the bulk of the normal diet. Yet so firmly ingrained in our thinking is the importance of furnishing full caloric requirements that restriction in this part of the diet is sometimes viewed with disfavor. Fortunately, the problem has interested many workers in the past few years and many data are now available as to the relative need for protein and calories under temporary conditions of restricted intake.



The studies on animals have been carried out by several groups of workers. For example, Allison et al.<sup>1</sup> found that the index of nitrogen balance in the dog was not altered until the caloric intake had been reduced to less than 50 per cent of normal. Benditt et al.<sup>2</sup> studied adult protein-depleted rats and found that the critical level of caloric intake above which the retention of nitrogen was not affected was about 70 per cent of the normal. These findings have been confirmed by Willman et al.<sup>3</sup> Analogous observations were made by Elman et al.<sup>4</sup> who were able to produce positive nitrogen balance in dogs on a restricted caloric intake provided the proportion of the protein component of the diet was increased considerably; when an isocaloric diet was given with a normal distribution between calories and protein of 80 to 20 respectively, nitrogen balance was not achieved.

In experiments on humans, Gamble and his coworkers<sup>5</sup> found that the losses of nitrogen following the ingestion of carbohydrate alone were reduced to a maximal degree by an intake of but 100 grams of glucose a day; an increase to 200 grams failed to spare any further tissue protein breakdown, and thus merely spared adipose tissue. More extensive observations in man were made by Schwimmer and McGavack.<sup>6</sup> Working with volunteers, they found that on a small intake of protein, i.e., 20 grams per day, increasing caloric intake definitely reduced nitrogen loss. However, when the protein intake was increased to 40 grams, nitrogen balance was improved, but there was no additional improvement on increasing the caloric intake from 900 to 1800 per day. They concluded, therefore, that with restricted diets, simple increase in the protein improves nitrogen balance far better than a similar increase in the caloric intake. Similar findings have been reported in humans given intravenous injections of glucose and amino acid mixtures.<sup>7</sup>

The implication from these studies would seem to be clear. If a restricted diet is necessary or advisable for any reason, this restriction should be limited to the calorogenic portion of the diet. In other words, a restricted diet in which the proportion of protein is relatively greater than normal will lead to better nitrogen balance than one in which the usual proportions are maintained. These findings thus confirm the theoretical considerations mentioned above, i.e., that adipose tissue will readily and safely furnish a good part of the energy requirements at least for limited periods of time whenever dietary restriction is necessary.

ROBERT ELMAN

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## HOW OFTEN IS THERE VALUE IN THE GIVING OF HYDROCHLORIC ACID?

Not infrequently one sees patients with indigestion who, after examination by some internist, were told that their troubles were due to gastric hypoacidity or anacidity, and were given dilute hydrochloric acid in doses of perhaps 20 drops after meals. In most such cases one learns that the symptoms continued unabated, and usually a little study of the patient suggests that the symptoms could better have been accounted for on the basis of some commonly met with condition, such as constitutional inadequacy, nervousness, hypertension, or menopausal depression.

The question then arises, does the internist who ascribes all the troubles of such a patient to achlorhydria know that he is getting rid of the man or woman with a placebo of diagnosis, or does he really believe that the failure of the stomach to secrete free acid after an Ewald meal, in a person past fifty, is always a sign of disease? He should read the chapter on this subject in Bloomfield and Polland's<sup>1</sup> book and note that perhaps 1 in 5 of older persons with no organic disease of the digestive tract show achlorhydria after an Ewald type of meal (p. 52). Using histamine as a stimulus, Polland<sup>2</sup> found that about 1 in 9 of 900 persons without carcinoma of the stomach or primary anemia failed to produce free hydrochloric acid. Vanzant and her colleagues<sup>3</sup> showed the way in which achlorhydria increases with age in men and women. By the age of 60 one in 4 or 5 had no acid. Others whose work might be consulted are Seidelin<sup>4</sup>, Dedichen<sup>5</sup>, Keefer and Bloomfield<sup>6</sup>, Sagal, Marks and Kantor<sup>7</sup>, Oliver and Wilkinson<sup>8</sup>, Ruffin and Dick<sup>9</sup>, and Rafsky and Weingarten<sup>10</sup>.

The next question is, when a physician prescribed a few minims of dilute hydrochloric acid, does he realize what a drop-in-the-bucket he is giving and how unlikely it is that with this tiny amount he will so change the pH of the gastric contents that pepsin will be activated and digestion be improved? Does he really think that a few drops of acid taken three times a day can do the work of the large quantities which are secreted in twenty-four hours by the healthy person? Perhaps he even prescribed a few drops of acid for a person who was still secreting a considerable amount. This is often done and naturally the results are usually or always nil, as one would expect them to be.

The probability is that in many cases the physician did not do much thinking, but in his search for something to explain the symptoms grasped at the first diagnostic straw that came along, and then treated it almost reflexly, as he had once been taught to do. Perhaps he was so anxious to reach some diag-

nosis that he accepted as significant and final one laboratory report of 10 or 15 units of free acid when more tests made at a time when the patient was less frightened at the sight of the stomach tube would have shown a normal acidity.

It is curious how strong a hold some few poorly based ideas get on textbook writers, medical students and physicians. Every student becomes so fascinated with these questionable ideas that he remembers them for life, no matter what else he forgets. One of these ideas is that achlorhydria commonly produces a morning diarrhea which can be relieved by the taking of a little hydrochloric acid. Actually, achlorhydria, which is present in 1 of 4 older persons, appears but rarely to be associated with diarrhea, and when there is diarrhea, it appears but rarely to be stopped by the taking of even large doses of acid. Just how little a few drops of dilute hydrochloric acid can accomplish has been shown by Crohn<sup>11</sup>, 1918, Kern, Rose and Austin<sup>12</sup>, Koehler and Windsor<sup>13</sup> and others.

According to Crohn (1918), Leo<sup>14</sup> was one of the first, in 1908, to estimate the value of giving hydrochloric acid. Although he gave from 75 to 225 minims at a time, he found that he could not make much difference in the acidity of the gastric contents. Crohn found that 20 minims of the dilute acid given in a single dose to a patient with achylia did not affect the acid titer of the digesting stomach. Repeated doses of from 25 to 40 minims had little more effect.

Koehler and Windsor, working in vitro, found that in order to bring the pH of an ordinary meal of milk, bread, meat, beans, peaches and potatoes to a fairly normal figure of 1.7 they had to add 34 cc., or 510 drops of dilute hydrochloric acid, U.S.P. Naturally, the stomach must secrete much more acid than this to maintain the acidity of the meal for two or three hours. Interestingly, Koehler and Windsor found also that the contents of even 20 capsules each containing 420 mg. of glutamic acid hydrochloride failed to produce a normal gastric pH such as would activate pepsin. The usual dose of, let us say, 2 capsules served to produce a pH of only 4.0, which would be useless because peptic activation begins at about pH 3.0 and does not amount to much until it drops to 2.0. The writers showed moreover that the amount of hydrochloric acid commonly given to patients cannot have any bactericidal effect such as might protect the person from intestinal infection.

In the presence of indigestion or abdominal discomfort, achlorhydria in most cases and especially in the cases of persons past middle age would appear to be a poor and inadequate diagnosis to make because the condition is so commonly only a sign of normal aging. As one would expect, then, it is usually symptomless. Many of the persons with an anacid stomach have the digestion of an ostrich. At times, of course, as when the achlorhydric patient has a tendency toward diarrhea, it may be well to try the effect of giving perhaps half a teaspoonful of dilute acid taken with meals. Kern, Rose and Austin advised the

giving of from 4 to 14 cc.! If such doses of acid do not immediately work a miracle, its use had probably better be given up. If it is going to help at all, it usually does so the first day. As Stafne<sup>15</sup> has pointed out also, the giving of much acid over a period of time usually removes the enamel from the lingual surface of the upper incisors.

Questions that arise nowadays are: (1) should hydrochloric acid be given regularly in the treatment of patients suffering from primary anemia, (2) will it reinforce the effects of liver extract, and (3) will it contribute something to the protection or regeneration of an atrophic gastric mucosa? Actually, it is hard to see why it should be given, especially when, as often happens, the patient's digestion is good. Older physicians know from their sad experience in the old days before liver extract became available that hydrochloric acid has no effect on primary anemias, and today there is no good proof that the giving of acid in small doses will improve the appearance of the gastric mucosa as seen through a gastroscope. Kern, Rose and Austin could not see that the long-continued taking of acid had any effect.

Always, when a gastroscopist feels tempted to write up some instances of a return to normal which he has observed in the gastric mucosa, he should re-read the excellent paper of Maimon and Palmer<sup>16</sup> in which they reported the changes in the appearance of the gastric mucosa which, in a group of persons, occurred from month to month, in the absence of treatment. Furthermore, it should be noted that in this group symptoms did not always come with the atrophic gastritis and did not always go when it cleared up.

In any effort to determine the value of hydrochloric acid as a remedy, the drug might well be given intermittently to see if the patient is regularly more comfortable when taking it and less well when not taking it. Always, it is possible for the patient to deceive himself through autosuggestion. It is helpful to know that if the acid is going to work a miracle it is likely to do so within the first 24 hours after its administration.

W. C. A.

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## METALLIC MERCURY IN THE DIGESTIVE TRACT APPEARS TO BE INNOCUOUS

Since a few gastroenterologists have been weighting intestinal balloons and the ends of tubes with a little mercury there has been some question as to what would happen if the apparatus were to break and spill the metal into the digestive tract. Fortunately, now, a 3-year-old boy has performed the necessary experiment to show that this accident need not be greatly feared. In the Bull. U. S. Army M. Dept. for October, 1948, p. 802, Lieutenant Colonel I. Louis Hoffman tells of a child who, while seated in the dental chair, was given 4 cc. of metallic mercury to play with. As might have been expected, he promptly swallowed it. To everyone's relief, it went through his digestive tract without doing any harm. For a while, much of it remained in the appendix. After nine days it was all out of the bowel.

As Hoffman said, besides this case there are others which indicate that metallic mercury in the bowel is inert and not absorbable. Birnbaum (Am. J. Surg., **74**: 494, 1947), however, has reported 1 case in which the metal stayed so long in the appendix that it apparently caused an acute inflammation, requiring prompt operative intervention.

W. C. A.

## THE ROLE OF ALPHA-TYPE STREPTOCOCCI (ENTEROCOCCI) IN FOOD POISONING

The isolation of alpha-type streptococci from foods incriminated in outbreaks of food poisoning, together with evidence obtained by experimental studies, strongly suggests an etiological role for these organisms. In 1926<sup>1</sup> strains of a streptococcus, one later identified<sup>2</sup> as *Streptococcus fecalis* of the Lancefield serological group D, were isolated in two episodes of food poisoning. One of the outbreaks was attributed to imported Albanian cheese and the other to American cheddar-type cheese. Buchbinder, Osler and Steffen<sup>3</sup> recently studied four outbreaks of food poisoning in which the available data seemed to implicate enterococci. Two of these outbreaks were attributed to milk products. Dack<sup>4</sup> investigated four outbreaks attributed to Vienna sausage, beef croquettes, coconut-cream pie and turkey dressing, in which alpha-type streptococci constituted the predominant organisms in the samples of food.

The symptoms of food poisoning could be produced in volunteers fed living cultures of the alpha-type streptococci isolated from the Vienna sausage and croquettes, but not in those individuals who ingested filtrates of the same cultures. One of these strains has been identified as *Streptococcus fecalis*.

As a rule, the clinical manifestations have been mild, consisting principally of abdominal cramping and diarrhea, and less frequently, nausea and vomiting. Further studies by Osler, Buchbinder and Steffen<sup>5</sup> indicated that two of four strains of *Streptococcus fecalis* were capable of producing symptoms of food poisoning in human volunteers when the living organisms were given in foods such as custards, egg salad and milk. The number of organisms present in food causing illness ranged from  $22.7 \times 10^9$  to  $148 \times 10^9$ . Uninoculated food failed to produce symptoms when eaten by the same volunteers. Linden, Turner and Thom have reported the production of diarrhea in cats by feeding milk cultures of *Streptococcus fecalis*. The mechanisms by which this organism produces symptoms of food poisoning when ingested by man are not known. Sherman<sup>6</sup> recently has discussed the current knowledge concerning the ability of *Streptococcus fecalis* to produce tyramine by the decarboxylation of tyrosine. This substance, as well as other amines, is known to cause symptoms of "ptomaine poisoning" when injected parenterally into man and animals. However, no evidence has been presented that these amines produce similar symptoms when given by the oral route.

This problem has been studied recently by Dack and his associates<sup>7</sup>. Experiments involving 52 feeding tests on 37 volunteers were carried out with the object of determining the safety of using a specific strain of *S. fecalis* as a starter culture for cheese. Feedings were made of cheese prepared with the starter strain (R2B), cultures of this strain, and, in addition, tyramine. Cultures from three strains of enterococci implicated in outbreaks of food poisoning were fed for control purposes. Cheese made with the starter strain of *S. fecalis* containing large numbers of viable organisms and appreciable quantities of tyramine was without effect. Tyramine monohydrochloride in 0.3 or 1.0 gram amounts, when fed in one pint of milk, likewise caused no untoward effects. Illness occurred in two and possibly another volunteer fed a milk culture of a strain of *S. liquefaciens* recently isolated from an outbreak of food poisoning. *S. fecalis*, in two strains from other outbreaks, was without effect when similarly fed to human volunteers.

The striking result in this investigation was the absence of symptoms in human volunteers fed large numbers of *S. fecalis* and considerable quantities of tyramine. Three of the four volunteers in one experiment involving *S. liquefaciens* became ill some time after drinking milk cultures containing 182 billion cells of strain R26. It is questionable whether the illness of one of the three subjects was related to the feeding. This individual was prone to de-

velop gastrointestinal symptoms during periods of emotional stress. The fact that 60 hours elapsed from the time of taking the test material would cast further doubt on the relation of the symptoms to the test feeding. In view of the fact that *S. fecalis* is a frequent contaminant in commercial cheese without causing illness, and in view of the aforementioned results, it was concluded that strain R2B of *S. fecalis* may be used safely as a starter culture in the manufacture of cheese.

The chief interest of these various studies, at present, is in directing attention to the possible role of enterococci in food poisoning. It seems clear from the observations of Dack that further investigation of the problem is desirable.

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## Comments

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*Readers are invited to contribute to the Comment Section of Gastroenterology short notes expressing their opinions on controversial topics and matters of current general interest.*

### CABBAGE JUICE AS A TREATMENT FOR ULCER

Since doctors are being asked about the new treatment of ulcer with cabbage juice, and since the paper was published in a state journal not easily available to many physicians, it may be well to make a note here about the new cure advocated by Garnett Cheney of San Francisco.

Cheney treated 13 patients, giving them at least a liter of fresh uncooked cabbage juice a day. The reason for giving this was that in guinea pigs, cabbage appeared to prevent the formation of ulcers due to histamine.

Cabbages were put in a juice press, and usually it took 2 kilograms of the raw vegetable to produce 1 liter of juice. The addition of celery juice made the cabbage juice more palatable. The last three patients treated were given a mixture of three parts of cabbage juice to one of celery juice. Salt and pepper and tomato juice should also be added. One in 3 of the patients had some abdominal distress and constipation, relieved by milk of magnesia. The juice was given 200 cc. at a time, five times a day. It was unpalatable if kept overnight. In addition to the cabbage and celery juice, a diet was given in which all of the food was cooked so as to destroy other sources of the supposed vitamin U. The patients were kept in bed until pain stopped. They were allowed to smoke. They were given sodium bicarbonate and codeine sulfate for the relief of pain, also sleep-makers at bedtime, and milk of magnesia to relieve constipation.

Cheney depended much on the roentgenologists to tell him when the ulcer was healed, and claimed that craters disappeared rapidly, often within two weeks. Many gastro-enterologists would not care to trust to this method or this criterion of ulcer healing. There were six gastric ulcers and one jejunal ulcer, all of which were seen with the gastroscope to heal rapidly. Cheney stated that the "anti-ulcer factor" is readily destroyed by heat. Wisely, he pointed out that the results are as yet only suggestive, and more work must be done.

Since November, 1948, a concentrate of cabbage fat prepared by Viobin Corporation of Monticello, Illinois, has protected guinea pigs from histamine-produced ulcers, when fed in doses of 100 mg. a day for a 300 gm. animal.



Naturally, the big question will be, will the healed ulcers stay healed any longer after this treatment than after other treatment?

W. C. A.

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## Book Reviews

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AN INTRODUCTION TO GASTROENTEROLOGY. *Walter C. Alvarez, M.D.* 4th Edition. Revised and enlarged. Paul Hoeber, Inc., New York, 1948, pp. 903.

As most physiologists and gastroenterologists know, this large volume contains a summary of practically everything of value which has ever been written on the motor functions of the digestive tract. Anyone who wants to get all of the information available on the movements of the stomach or bowel or the extrinsic or intrinsic innervation of the digestive tract, or the functions of the cardia or pylorus or ileo-cecal sphincter, or the mechanism of the emptying of the gallbladder can go to this volume and find what he needs.

Thus Chapter 29 contains all the information available in regard to gas in the bowel and flatulence. Chapter 33 is on technical methods and apparatus and Chapter 34 is on books and reading and where to go in the library to get information in regard to the functions of the stomach and intestine. For years librarians have kept a copy of this book handy so that if someone comes in and asks, "Where can I find Graham and Cole's original article on the roentgenologic examination of the gallbladder," or "Where can I find Bayliss and Starling's classic paper on the reflexes of the small bowel?" the librarian can immediately hand out the information.

Now a new edition has come out which has been brought up to date with information derived from some 400 new articles and books. The bibliography now runs to some 2,800 titles. The heaviest additions have been made to the chapters on the pylorus, the nerves running to the bowel, the nerves to the gallbladder, the functions of the colon, flatulence, the electro-enterogram and technical methods and apparatus. Because of the present day interest in the Dragstedt operation, there is much on the effects of vagotomy in animals and man. Some 125 pages of text have been added.

One great advantage of this book is that it brings together in one place all the information that can be obtained from the literature of the anatomists, the physiologists, the chemists, the comparative anatomists and physiologists, the roentgenologists, the surgeons and the clinicians.

With the idea of saving the time of the student and the busy practitioner of medicine and surgery, who may want to have a brief answer to some question, Alvarez has added to each chapter a summary of the information contained.

As Alvarez has said, the literature of science has become so enormous that whenever possible, older men who have a thorough knowledge of the subject should try to help younger men with their reading. As he said, "We must lift them up and start them off on the level of our intellectual shoulders. Obviously they cannot begin by reading all that we have read in forty years. That small part which we have found useful should be taken out and summarized for them. We must show them where to look in the library for the most important papers, books and review articles."

This is the sort of reference book that every medical library must have, and every serious student of physiology and gastro-enterology will want to have within reach.

As suggested by the title, any young man who plans to make his career in gastro-enterology will do well to prepare himself by reading this volume, filled as it is with the scientific gleanings of a man who for forty years has read avidly in several languages.

MAGIC IN A BOTTLE. *Milton Silvermann, M.D.* Macmillan Company, New York. Second Edition. 1948.

This delightful book now appears in the second edition. Silvermann has done a tremendous amount of research to find the original articles about a large number of commonly used and most valuable drugs. He writes well and interestingly, and every physician who reads this book will become a better educated person. This is another book to put by the side of the bed for the last half hour of the day. We physicians are all indebted to Dr. Silvermann for his splendid piece of research and writing.

THE PLAGUE AND I. *Betty Macdonald.* J. B. Lippincott Company, Philadelphia, pp. 254.

It can always be very instructive to a physician to read the impressions of an intelligent, keenly observant patient as he or she undergoes examination and treatment. In this way one learns of many things in the patient's environment, and in his or her handling, which are bad and unfortunate, and which do harm not only to the patient but to the cause of medicine, and to the reputation of the physician in charge. For this reason it is always well for physicians to read books such as THE PLAGUE AND I.

Often to a physician a patient is only Mrs. So and So with a number who has got a disease. The disease is treated and the woman with all her fears and tremendous impressions and discouragements is not even thought of. In this book one gets some impression of what goes on inside of the mind of the patient who is suddenly faced with the need for giving up work and great responsibilities, and going to bed for months or years. One comes to realize what it means to be in the power of an unpleasant nurse, or a cold blooded physician, or to lose one's privacy. One gets an insight also into the terrible problems of the patient who comes out of the hospital and has to find his or her place in life again; to get a job and to live down the fact that he or she has been in a sanatorium.

THE SURGERY OF THE STOMACH AND DUODENUM. *T. H. Somervell, B.Ch., F.R.C.S.* (Eng.). The Williams and Wilkins Company, Baltimore, 1948, pp. 546, price \$11.

This is a very attractive book written by an unusual man. British surgeons know him well as a man who has done splendid work in the Mission Hospital of Neyyoor, South India. Mountaineers will remember him as a man who climbed high up toward the top of Mt. Everest. Others know him as an artist. Many American surgeons will recognize him as a man who suggested that one of the best treatments for peptic ulcer is the tying of most of the arteries supplying the stomach.

It is remarkable to find a man, and especially a busy man working so far away from the beaten path of science, writing such a fine book, and one filled with so much up-to-date information.

On page 265 to 276 one finds a discussion of Dr. Somervell's operation of devascularization of the stomach. He ties first the vessels on the anterior surface of the stomach; then the sheaf of vessels running down the lesser curvature; then the small branches from the right gastric artery, but not those within an inch and one-half of the pylorus. He never ties the main left gastric artery. An opening is then made in the mesocolon and through this window all the vessels near the lesser curvature, which can be reached easily, are tied. Then the remaining vessels on the greater curvature are tied, thus bringing the number ligated to five out of every six vessels. The appearance of the body of the stomach should then be "thoroughly unhealthy." If it still looks healthy in color, the main gastroepiploic artery should be tied in two places, about two inches from the pylorus. The stomach will then be yellowish in some places and purplish in others, and the surgeon will be afraid to return the viscus to the abdomen. In spite of this, in most cases Dr. Somervell goes on and does a posterior gastrojejunostomy.

He says that Wilson Hey introduced this operation. He divides the greater and lesser omenta from the stomach throughout their whole length except for the  $1\frac{1}{2}$  to 2 inches nearest the pylorus. Hey doubted if this operation was as good as gastrectomy for the cure of ulcer. It should not be used in cases of gastric ulcer. In 71% of the cases done by Dr. Somervell, the acid was greatly reduced and almost permanently so.

American surgeons have not been enthusiastic about this operation partly because the tying of the gastric arteries in dogs has failed to show much effect on acidity and partly because there have been a few cases in which the stomach sloughed. Somervell states his impression that there must be some particular reason why this operation works best on his Indian patients. He says that there has been very little trouble with jejunal ulcer after the operation.

Dr. Somervell is to be complimented on having written a useful book.

THE MODERN MANAGEMENT OF GASTRIC AND DUODENAL ULCER. Edited by F. Croxon Deller, M.D. The Williams and Wilkins Company, Baltimore, 1948, pp. 227, price \$5.50.

This book by several able Englishmen is well written and well illustrated. It deals with both medical and surgical forms of treatment. On page 79 Deller tells of the work of Hermon Taylor (1946) who reported 28 consecutive cases of acute perforation of an ulcer, in which the treatment was restricted to frequent evacuation of the stomach by tube and suction. Twenty-four of the patients made an uneventful recovery. All of the perforations save two were duodenal in origin. This treatment is probably most likely to result well when the perforation occurs when the stomach is empty.

The book is attractive and doubtless will be read with pleasure and profit by many American gastroenterologists.

DISEASES OF THE ADRENALS. *Louis J. Soffer*. Second Edition, thoroughly revised. Lea and Febiger, Philadelphia, 1948, 320 pp.

Dr. Soffer of Mt. Sinai Hospital in New York City has put all internists in his debt by his summarization, in an attractive manner, of the enormous amount of work which has been done in recent years on the adrenal glands and their function in health and disease.

Most interesting to the gastroenterologist will be the information given on pages 114 and 115. As everyone should know, quite a few patients, especially in the early stages of Addison's disease, go to the gastroenterologist because of some loss of weight and strength, and particularly loss of appetite. In these cases the coming of gastrointestinal symptoms suggests the presence of extensive destruction of the adrenal cortex. Many of these persons with skin pigmentation, low blood pressure, and feelings of fatigue get along fairly well for years. Then they may begin to have persistent or recurrent attacks of indigestion, and this means a serious threat to life. Usually they begin with loss of appetite and later they get nausea, and perhaps episodes of vomiting, and constipation. Occasionally there will be abdominal pain and diarrhea. Usually the abdominal pain is of a vague character, but occasionally it may be severe. It may be of the hunger type, relieved by food and alkalies. In bad cases there may be some gastritis. There have been cases in which the gastric mucosa bled from small ulcers. A few patients will crave salt.

These patients usually show hypoacidity or actual achlorhydria. Achlorhydria was observed in 50 per cent of Soffer's group of patients. Loss of body weight is common and characteristic. This may average around 20 to 30 pounds, but it may range up to 60 pounds.

Very important are the crises in Addison's disease which must be recognized quickly if the patient's life is to be saved. The patient may think that he has eaten some bad food that made him very ill. There will be nausea, vomiting and diarrhea, sometimes severe and intractable. This goes on until the patient collapses.

Naturally, it is highly important to make the correct diagnosis because an operation done on a patient with untreated Addison's disease practically always means death.

The discussion of the pheochromocytomas, on pages 290 and 292, is important. The picture of paroxysmal hypertension is often a puzzling one, and the diagnosis may be missed. Often the tumor can be felt in one or other kidney fossa.

THE SURGERY OF ABDOMINAL HERNIA. *George B. Mair*. The Williams and Wilkins Company, Baltimore, 1948, 408 pp.

This book, written by a British surgeon, is very attractive. It is well written, well illustrated, and is based on a good deal of research. It is to be recommended.

STUDIES IN PSYCHOSOMATIC MEDICINE. *An Approach to the Cause and Treatment of Vegetative Disturbances*. Edited by Franz Alexander and Thomas Morton French. The Ronal Press Company, 1949, pp. 568, price \$7.50.

This large volume of 568 pages is a collection of a number of articles published in

the past by members of the staff of the Chicago Institute for Psychoanalysis. Perhaps one of the most valuable of the articles is by Roy R. Grinker on Hypothalamic Functions in Psychosomatic Interrelations.

Most of the articles are concerned with an analysis of the mental make-up of persons with the several diseases. Unfortunately, in most instances not enough cases were studied, and hence it is questionable how much was learned. For instance, how is anyone going to know if there is any particular mental make-up connected with hypertension until someone has studied many patients from many racial groups. Thus, a while ago a study was published on the hypertension mentality of a group of foreign born Jews found in a New York Clinic. Many of them were fearful, down-trodden, mother-dependent, hen-pecked individuals, who had been kicked about all their lives and showed it. One wonders if the authors would ever have reported their study if they had analyzed also the mental make-up of a few dynamic, powerfully built and hard driving hypertensive executives in some of our big national companies.

A similar defect is to be found in the articles now appearing on an analysis of a few persons with peptic ulcer or ulcerative colitis or other gastro-intestinal disturbance. This sort of analysis was attempted by Franz Alexander in a large chapter in this book. One wonders how much value these studies have when made on highly psychotic persons by someone with a profound Freudian trend. Certainly, as yet they have no value to the average physician. To begin with, he probably won't read the reports and if he did, he would feel strong revulsion against some of the interpretations advanced. He would say, "I never saw such screwy patients in my life, and I can't see what bearing their queer ideas have on my diagnostic problems." Certainly, the non-psychiatric physician needs to get much more interest in psychiatric problems but he needs mainly help with the persons who are struggling with the common ordinary simple problems of life, such as overwork, strain, tension, grief, and financial and marital difficulties. He does not need to worry about the girl who wants to bite off her father's penis!

Because this book has so little to say about the doctor's practical problems, it will not be of much interest to the average physician.

# ABSTRACTS OF CURRENT LITERATURE

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## STOMACH

FINKELSTEIN, C. Zur frage der behandlung des inoperablen Magenkrebses mit Auto-vaccinationen von Magensaft des Kranken [Treatment of inoperable gastric carcinoma by autovaccination with the patient's gastric juice] *Gastroenterologia*, 73: 45 (1948). Historically, numerous attempts have been made to immunize patients with gastric carcinoma with vaccines which were prepared from the patient's tumor. The author's proposed technique consists of a series of injections of specially prepared gastric juice obtained from the patient and administered two or three times weekly in increasing quantities. In a series of 20 patients with advanced gastric carcinoma, it was believed that the length of life was prolonged. Improvement in appetite and weight were observed, and pain was decreased. An increased sense of well-being was noted. Further trial of the treatment in a larger series of cases is recommended.

CHARLES A. FLOOD.

PETERMANN, M. L. AND HOGNESS, K. R. Electrophoretic studies on the plasma proteins of patients with neoplastic disease. I. Gastric cancer. *Cancer*, 1: 100 (May) 1948.

The authors present electrophoretic studies of the plasma proteins in patients with gastric ulcers and carcinoma. Their investigations disclose that, in gastric ulcer and carcinoma, the hypoproteinemia is due to a decrease in albumin alone. However, in gastric ulcer, the other components are normal, whereas in carcinoma the gamma globulin and fibrinogen are somewhat increased. After resection of the tumor, the latter components return to normal within a few weeks. The restitution of albumin is extremely slow even in patients maintained in positive nitrogen balance.

DAVID A. DREILING.

PETERMANN, M. L. AND HOGNESS, K. R. Electrophoretic studies on the plasma proteins of patients with neoplastic disease. II. An acid protein present in the plasma. *Cancer*, 1: 104 (May) 1948.

Electrophoretic analysis of human plasma showed that, in patients with gastric carcinoma, pulmonary carcinoma, and other neoplastic diseases, there is a significantly greater quantity of an acid protein than is found in the plasma of normal subjects. Following gastrectomy for carcinoma, this increased quantity of the protein disappeared in 6 patients studied.

DAVID A. DREILING.

MALENCHINI, M. AND ROCA, J. Tumors of the upper third of the stomach. *Am. J. Roent. Rad. Therapy*, 60: 323 (Sept.) 1948.

The upper third of the stomach is situated deep in the left hypochondrium; it is inaccessible to palpation under the roentgenological screen. Also, the contrast substance, when the examination is made in the vertical position, passes rapidly through this part without stopping; in routine examinations in the Trendelenburg position, the abundant quantity of spreading barium hides any tumors that may be present, unless they are marginal or have reached considerable size. The existence of an air bubble in the stomach favors the discovery of tumors of this part. In this space, the tumor is projected as a soft tissue shadow that alters its outline. When the air bubble does not exist or its shape and size are unusual, the radiologist can create or exaggerate it by injecting gas. Notwithstanding their great value, the soft tissue shadows that can be observed in the air bubble may lead to an error. The tumors located in the upper third of the stomach often alter the esophagus, affect the stream of barium entering the stomach, and produce filling defects of different localization.

FRANZ J. LUST.

PALMER, E. D. The gastroscopic picture in post-irradiation gastritis. *Am. J. Roent. Rad. Therapy*, 60: 360 (Sept.) 1948.

Gastroscopic studies in 12 patients, who had developed post-irradiation gastritis following intensive radiation treatment for malignant disease, showed remarkably constant and characteristic gastric changes. The picture included marked edema with tubular deformity and fixation of the antrum, similar fixed patulousness of the pylorus, and clean deep chronic ulcers which healed without contraction. Following subtotal gastrectomy with posterior gastroenterostomy, the picture was that of the normal postoperative stomach. Pathologic and roentgenographic studies in general corroborated the gastroscopic findings. A new gastroscopic entity is presented, but, because the diagnosis of post-irradiation gastritis should be obvious from the history, the importance of endo-

scopy lies in the evaluation of the severity of the radiation damage.

FRANZ J. LUST.

ULFELDER, H., GRAHAM, R. M., AND MEIGS, J. V. Further studies on the cytologic method in the problem of gastric cancer. *Ann. Surg.*, 128: 422 (Sept.) 1948.

These authors describe their procedure for obtaining cells from the stomach for diagnostic study, by washing its lumen with normal saline solution. Forty-eight patients have been studied in this fashion. In 3, the specimens were unsatisfactory due to gastric retention associated with obstruction at the pylorus. Of 14 patients who were found to have carcinoma of the stomach at operation, 12 were correctly diagnosed before operation by the study of aspirated cells. A false positive diagnosis by the cytological method was obtained in one instance.

LEMUEL C. MCGEE.

## BOWEL

WEINBERGER, H. A. AND PALTAF, R. M. Tumors of the small intestine. *Surgery*, 23: 35 (July) 1948.

In spite of the rarity of small bowel tumors, the authors have compiled a report of 20 cases seen in a large hospital over a period of 40 years. The distribution of cases, duration of symptoms, clinical signs and symptoms, X-ray findings, and pathologic features of these cases are presented. Detailed case studies on 2 cases of malignancy are included in order to demonstrate the problems which malignant neoplasms of the small bowel involve. These authors feel that malignant neoplastic lesions should be considered by both clinician and surgeon when analyzing vague gastrointestinal complaints in any age group or in obscure gastrointestinal bleeding, and that laparotomy should be resorted to more frequently in those cases where diagnostic studies are not conclusive.

FRANCIS D. MURPHY.

SUNDERLAND, D. A. AND BINKLEY, G. E. Papillary adenomas of the large intestine. *Cancer*, 1: 184 (July) 1948.



In a series of 3356 cases with large intestinal tumors, 48 cases with polypoid adenomas were found and studied by the authors. Papillary adenoma is considered as a distinct clinical entity lying midway between benign adenoma and adenocarcinoma. It is believed to be a growth variant of the common mucosal adenoma occurring in the older age groups. Such tumors are found most frequently in the rectum, and may reach huge sizes. Clinically, the rate of growth is extremely slow and there is a marked tendency to repeated recurrence after removal. Among the cases studied by the authors, 68 per cent showed carcinoma in situ or in a recurrence. Because of the evident malignant potentialities, it is suggested that the rectum should be resected in all cases with cell atypism when complete local excision is impossible. Repeated fulguration should be reserved for those tumors with entirely benign structure.

DAVID A. DREILING.

BEST, R. R. Management of the ileosigmoidal fistula in diverticulitis. *Surgery*, 23: 30 (July) 1948.

Four cases of acute diverticulitis of the sigmoid, resulting in the formation of ileosigmoidal fistula, are presented. Immediate relief was accomplished by enterenterostomy around the inflammatory mass and colostomy of the transverse colon. Further surgery is indicated by the change in the pathologic condition and the wishes of the patient.

FRANCIS D. MURPHY.

WYATT, G. M. Barium sulfate in saline suspension. Examination of the colon in the presence of partial obstruction. *Radiol.*, 51: 326 (Sept.) 1948.

There is a small group of patients, with symptoms of unexplained rectal bleeding or abdominal tumor, who present an unusually difficult diagnostic problem to the roentgenologist. These patients fall into two categories: 1) those who cannot retain an enema because of a relaxed or damaged anal sphincter or perineum; and 2) those who do not have clinical obstruction or dilatation of the intestine, but who present complete obstruction to the retrograde passage of a

barium enema. It is with the latter group of patients that this paper is primarily concerned. Many of these patients have diverticulitis, and a small percentage also have rectal bleeding due to diverticulitis.

Oral administration of barium in the presence of obstruction of the lower bowel is considered dangerous because of the probability of dehydration and impaction. Even normal patients have often difficulty in expelling the barium. One logical method of preventing dehydration of the barium is to administer it with a saline cathartic which, by its nature, maintains and increases liquefaction of the contents of the colon. The author's method is to have the patient hospitalized. Four ounces of barium sulfate is mixed with 8 ounces of magnesium citrate. This mixture is given orally early in the morning and the patient is allowed water ad lib. Another 8 ounces of magnesium citrate, without additional barium, is given about 1½ hours later. Fluoroscopy is done at intervals starting about 2 hours following the administration of the barium. The speed of the passage of the barium-saline mixture varies markedly with the degree of obstruction and the age and physical activity of the patient. Excretion is usually almost complete at the end of eighteen hours. Such patients must obviously be kept under roentgenological observation until the barium is excreted and should be kept in the hospital for facilitation of such observation. Roentgenograms, demonstrating cases of neoplasms and diverticulitis, illustrate the author's method.

FRANZ J. LUST.

BELL, J. C. AND DOUGLAS, J. B. Roentgen-ray diagnosis of malignant and potentially malignant lesions of the colon and rectum. *Radiol.*, 51: 297 (Sept.) 1948.

The authors stress the importance of careful preparation of the patient for the roentgenological examination. They insist on a low residue diet and 1½ to 2 ounces of castor oil before the evening meal prior to the X-ray examination. On the morning of the examination, a warm tap-water enema is given. The authors use a spot-film device. Films are taken at different angles. The double-contrast enema method is best for

the demonstration of intestinal polyps. Some films are taken straight lateral, showing the anterior and posterior wall of the rectum. The early diagnosis of intestinal cancer, before an obstruction occurs, is stressed. Ten figures demonstrate the pathology of the rectum and sigmoid.

FRANZ J. LUST.

PENDERGRASS, R. C. Extrinsic deformities of the colon. *Radiol.*, **51**: 320 (Sept.) 1948.

The author classifies the causes of extrinsic deformities of the colon as follows: 1) enlarged viscera, including tumors of these viscera; 2) inflammatory processes, adhesions and endometriosis; 3) retroperitoneal tumors, mesenteric tumors, and omental tumors; 4) tumors of the colonic wall, not invading the mucosa; and 5) intra-abdominal and inguinal hernia. Instructive roentgenograms are included in this article. Cases discussed include: depression of the hepatic flexure by carcinoma of the kidney, aspect of colon before and after drainage of a perirenal abscess, appendiceal abscess, leiomyosarcoma of the colonic wall, ileo-cecal tuberculosis, and internal hernia simulating displacement by intra-abdominal masses.

FRANZ J. LUST.

OWENS, F. M., JR. Regional enteritis—Further pathological observations. *Arch. Surg.*, **57**: 195 (Aug.) 1948.

It is well recognized that regional enteritis is protean in its clinical manifestations. The pathologic observations vary considerably, in accordance with the duration and severity of the symptoms. Just as Hodgkin's disease is diagnosed by no one single microscopic criterion, so also is regional enteritis diagnosed by the coexistence of several pathologic changes. The bowel wall is invariably thickened by edema and fibrosis in regional enteritis, in contrast to the decided thinning of the wall often seen in ulcerative colitis. The serosa is thickened and the areas of involvement are demarcated by the extension of mesenteric fat over the serosal surface of the bowel. The mesentery is thickened by extensive edema and contains many large hypertro-

phied lymph nodes. Cut sections reveal that the edema involves all of the coats of the bowel wall, but is most marked in the submucosal layer. Ulcers are present but there is not the extensive necrotizing, sloughing, deep ulceration which is typically seen in ulcerative colitis. Individually, the processes represented in the total "picture" of regional enteritis are not unique. It is the repetition of the "picture" in conjunction with its stereotypy in case after case of clinically typical regional enteritis which supports the contention that this is a clinical pathologic entity.

ALBERT CORNELL.

HOXWORTH, P. I. AND SLAUGHTER, D. P. Polyposis (adenomatosis) of the colon. *Surgery*, **23**: 188 (Aug.) 1948.

Polyposis (adenomatosis) of the colon, while relatively rare, is a condition of interest because of its familial and congenital aspects, the diffuse involvement of the colon, and the marked tendency to malignant change at an early age. This article contains an historical review concerning the pathology, genesis, and behavior of the disease as well as a description of the experience of surgeons in the operative management. In addition, 7 new cases of polyposis are included which illustrate differences in surgical approach, as determined by preoperative studies and by present-day concepts of the disease and its management. Treatment of this condition is dependent upon its recognition and differentiation from other diseases. Surgery is directed toward either total ablation of the large bowel or total colectomy, and ileosigmoid (ileorectal) anastomosis combined with fulguration of polyps in the preserved segment. Prognosis has improved with earlier recognition of the disease and modern surgical, especially intestinal, procedures.

FRANCIS D. MURPHY.

HOPKINS, F. S. AND TATE, R. C. Carcinoma of the rectum. *New Eng. J. Med.*, **239**: 501 (Sept.) 1948.

This paper is a statistical study of 112 cases of cancer of the rectum treated surgically more than 5 years ago. There were 81 men

and 31 women, whose average age was 67 years, the majority of cases occurring during the sixth and seventh decades. After reviewing the symptoms and the means of diagnosis of the disease, the authors outline the preoperative preparation. The results obtained by various operative procedures are evaluated. While the number of cases in this series is small for statistical purposes, certain general conclusions may be drawn. There has been a steady drop in operative mortality since 1942, attributable to chemotherapy and better understanding of body chemistry. The Miles one-stage abdominoperineal operation is the procedure of choice in most cases of cancer of the rectum. There is apparent cure of 81.2 per cent of patients without obvious metastases, who did not die of other causes. Those who survive lead normal lives and are not significantly hampered by a colostomy. Many more patients could be placed in this relatively fortunate group if every physician would make an adequate rectal examination whenever a patient reports a change in bowel habits or rectal bleeding.

ANTHONY M. KASICH.

STAFFORD, E. S. AND SCOTT, H. W., JR.

The mortality of appendical perforation.

Southern Med. J., 41: 834 (Sept.) 1948.

The progressive decrease in mortality from 10 to 7 per cent from appendical perforation during the last 20 years is attributed by the authors to the following, in the order of their importance: 1) maintenance of fluid and electrolyte balance; 2) gastrointestinal decompression by the Miller-Abbott tube or its various modifications; 3) improved recognition and treatment of the complications of appendical perforation, notably mechanical ileus and subphrenic abscess; and 4) the use of chemotherapy and antibiotics, which have played an especially important part in reduction of morbidity.

The authors analyze 23 cases, which terminated fatally, in a series of 325 patients with appendical perforation during the period 1939-1947, and compare results with data from 479 similar patients during the period 1931-1939. While the means of treating this complication have improved, there has been no improvement in diagnosis,

and the incidence of delayed hospitalization has not been altered. Only by education of the public and the physician can deaths from this cause be further decreased.

ANTHONY M. KASICH.

CLARK, R. L., JR. Selection of treatment in advanced carcinoma of the rectum.

Southern Med. J., 41: 765 (Sept.) 1948.

There has been a remarkable improvement in results of operative treatment for cancer of the rectum in the last few decades. Today, operation in over 60 per cent of diagnosed cases results in survival of over 90 per cent of this surgically treated group. After five years, 50 per cent of these are still alive. These results are due not only to improvement in surgical technic, but also to the widespread use of chemotherapy, blood and blood substitutes, methods of mechanical decompression of the bowel, and the parenteral use of concentrated nutrients and vitamins.

After discussing various operative procedures heretofore used in cancer of the rectum, the author gives a detailed description of a two-stage anterior and posterior resection which seems to promise better results. Among the advantages claimed for the operation are the extended range of operability and the fact that only a single-barrel colostomy is left. In advanced lesions there is an opportunity of re-establishing the continuity of the bowel at a later date without jeopardizing the life of the patient or increasing the danger of recurrence by doing a temporizing procedure.

Eight figures illustrating the technic of the operation, and two case reports are included.

ANTHONY M. KASICH.

LOCKWOOD, I. H., SMITH, A. B., AND WALKER, J. W. Acute small intestinal obstruction. Radiol., 51: 310 (Sept.) 1948.

In all of the authors' reported cases of small bowel obstruction, the cardinal symptoms of intestinal colic and vomiting were present. The term, intestinal colic, refers to the concomitant occurrence of borborygmi at the acme of pains. Abdominal distention was present in most of the cases. With the

earliest roentgen sign of small intestinal obstruction and a clinical story of obstruction, the authors believe that surgery is immediately necessary. A single loop obstruction may also mean that the blood supply to a segment of gut is embarrassed if the normal anatomical markings are not clearly defined. Valvulae conniventes are present throughout the small intestine. In gangrene, the bowel quickly loses tone and becomes edematous, its physiological pattern rapidly disappears, and it becomes a smooth-walled tube distended with gas. Another sign is single or multiple "C-shaped" loops of small intestine arising from a common source or pedicle. This pattern is accompanied by a loss of the valvulae conniventes. In no case should we try to correlate the degree of distention seen on a roentgenogram with the severity of the symptoms.

FRANZ J. LUST.

#### LIVER AND GALL BLADDER

MOORE, G. E. AND SMITH, M. J. Intravenous cholecystography with tetraiodophthalic fluorescein. *Surgery*, **23**: 17 (July) 1948.

Twenty-two patients were examined by means of intravenous cholecystography utilizing tetraiodofluorescein in dosage of approximately 40 mg. per kilogram. This method of roentgenologic examination was found simple, rapid, and nontoxic; the optimum time of visualization being 2-3 hours after injection. The authors report a minimum of preparation necessary to obtain good cholecystograms.

FRANCIS D. MURPHY.

ERNST, R. G. AND DOTTI, L.B. An evaluation of the thymol turbidity test. *Am. J. Med. Sci.*, **216**: 316 (Sept.) 1948.

Thymol turbidity tests on 500 supposedly normal subjects gave results between 0 and 3.0 units in 87 per cent of the group. Tests on 527 patients, admitted to the hospital and diagnosed as having disease not commonly considered to involve the liver, showed 66 per cent to be in the range from 1.0 to 6.4 units of thymol turbidity. In virus pneumonia, infectious mono-

nucleosis, sickle cell anemia, secondary syphilis, and malaria in crisis, elevated readings were obtained. Of 477 determinations on 124 patients with liver or biliary tract disease, 360 (75.5 %) showed thymol turbidity readings ranging between 5.1 and 38.6 units. Infectious hepatitis gave the highest readings; the maximum readings occurring about the 14th day of illness and just prior to the maximum icterus. The thymol turbidity tests parallel the cephalin-cholesterol flocculation tests quite well in cases of parenchymal liver disease.

The ingestion of a meal or refrigeration of the sera over long periods of time has little influence on the thymol turbidity test. Inactivation, by heating sera at 56°C. for 30 minutes, lowers the turbidity readings by an average of 2.5 units.

LEMUEL C. MCGEE.

POPPER, H. AND STEIGMANN, F. Differential diagnosis between medical and surgical jaundice by laboratory tests. *Ann. Int. Med.*, **29**: 469 (Sept.) 1948.

A series of 285 cases of jaundice are evaluated, in order to develop a pattern for differential diagnosis and eliminate unnecessary surgical procedures or delay of operation. Current laboratory methods are discussed, and their practical value determined. Diagnosis is based on the two cardinal factors, liver cell damage and marked interference with bile flow. For diagnosis of the vast majority of cases of medical jaundice, four tests are deemed necessary: cephalin-cholesterol flocculation, thymol turbidity, albumin-globulin ratio, and cholesterol ester/cholesterol ratio. Positive results of a combination of two tests are regarded as diagnostically significant. Addition of the thymol turbidity test has greatly reduced the necessity for more complicated liver function tests. Most consistently, the correct diagnosis of surgical jaundice (mechanical interference with bile flow) was determined by serum alkaline phosphatase and urinary urobilinogen determination. The positive results of either test are considered significant. The exception is jaundice after treatment with arsenicals, producing marked interference with bile flow without detectable liver damage;

in such cases the patient's history will be of help. Cephalin-cholesterol flocculation serves as a link in cases exhibiting evidence of parenchymal liver damage and also interference with bile flow. Positive cephalin-cholesterol flocculation would classify the case as medical jaundice; a negative test would indicate that the liver cell damage may be secondary to biliary obstruction, and as such require surgery.

L. T. ROSENTHAL.

PARTINGTON, P. F. AND SACHS, M. D.

Routine use of operative cholangiography.

Surg. Gyn. Obs., 87: 299 (Sept.) 1948.

The authors' results with the routine use of operative cholangiography, on all patients requiring gallbladder or common duct surgery during 1946-1947, are presented. The type of patients in which operative cholangiography has proved successful is discussed. Operative cholangiography is directly dependent upon the ability to produce a cholangiogram of good diagnostic quality with a negligible loss of time. In the past, poor films, insufficient information obtained, and excessive time consumed in examination, were common objections. These objectionable features have now been remedied.

FRANCIS D. MURPHY.

BEST, R. R. The quantitative and qualitative control of bile flow and its relation to biliary tract surgery. *Ann. Surg.*, 128: 348 (Sept.) 1948.

In a discussion of the recurrence of biliary tract stones following cholecystectomy, Best examines the influence of the character of the bile flow. To some extent the quality of the bile can be influenced by the use of triketocholanic acid (dehydrocholic acid). In the experimental work of several investigators, it has been found that dehydrocholic acid not only increases bile flow but produces a less viscous bile. If stasis in the biliary tract is a factor in the intraductal plugging by debris and in stone formation, it is not difficult to conclude that a thin, watery bile resulting from the administration of hydrocholeretics may be beneficial to the postcholecystectomy patient.

Under this reasoning Best, since 1936, has

directed his postcholecystectomy patients to use hydrocholeretics for 2 or 3 days, once or twice each month, to obtain a "biliary flush". Patients operated upon previous to 1936 did not practice the periodic use of a hydrocholeretic. Only 82 per cent of this group of 48 patients had no recurrence of symptoms. In 60 patients receiving cholecystectomy since 1936 and having the "biliary flush" at monthly intervals or oftener, 94 per cent have been symptom-free. Best suggests that the postcholecystectomy syndrome in some of these patients may have been avoided by the use of hydrocholeretics.

LEMUEL C. MCGEE.

COLE, W. H., REYNOLDS, J. T., AND IRENEUS, C., JR. Strictures of the common duct. *Ann. Surg.*, 128: 332 (Sept.) 1948.

With a group of 49 patients undergoing surgery because of stricture of the common bile duct, previous operative trauma could be identified as the direct cause of the stricture in 32 instances (65%). In 5 patients (10%), the stricture was thought to be due to chronic pancreatitis of the fibrosing type. In 11 patients (23%), the mechanism of stricture formation was not obvious. One patient had a stricture as a result of a pancreatic cyst.

Operative repair technics are described. The best results—86 per cent satisfactory—were obtained in instances of local stricture repaired by end-to-end anastomosis. The most difficult type of stricture for repair was the one in which no duct could be found except at the hilus of the liver.

LEMUEL C. MCGEE.

## PANCREAS

GAMBILL, E. E. AND PUGH, D. G. Pancreatic calcification. Study of clinical and roentgenologic data on thirty-nine cases. *Arch. Int. Med.*, 81: 301 (Mar.) 1948.

The authors studied 39 cases of pancreatic calcification, selected solely on the basis of roentgenological evidence. In this group, calcareous deposits in the pancreas usually were associated with relapsing pancreatitis.

Although the most common symptomatology was that of pancreatitis, this was doubtful or lacking in 2/5 of the cases. Associated complications included diabetes, steatorrhea, gastrointestinal hemorrhage, pancreatic pseudocyst, pancreatic abscess and peripheral neuritis. Morphine often resulted as a result of severe pain. There was a high degree of positive correlation between the extent of the pancreatic calcification and the incidence of diabetes and steatorrhea. These complications occurred only in those cases of calcification in which there was a definite diagnosis of pancreatitis.

EDGAR WAYBURN.

GOLDSTEIN, N. P., EPSTEIN, J. H., AND ROE, J. H. Studies of pancreatic function. IV. A simplified method for the determination of serum lipase, using aqueous tributyrin as substrate, with one hundred normal values by this method. *J. Lab. Clin. Med.*, **33**: 1047 (Aug.) 1948.

The authors have developed a modification of the serum tributyrinase method for the determination of serum lipase which eliminates the use of bile salts. They employ tributyrin, properly homogenized in an aqueous digestion mixture buffered with sodium diethylbarbiturate. The titration of the fatty acid is carried out either with phenolphthalein as the indicator or electrometrically. The serum tributyrinase level of 100 normal subjects was determined. The normal range varied from 85 to 205 tributyrinase units, with values for males generally higher than those for females.

EDGAR WAYBURN.

## ULCER

DUNPHY, J. E. AND HOERR, S. O. The indication for emergency operation in severe hemorrhage from gastric or duodenal ulcer. *Surgery*, **23**: 231 (Aug.) 1948.

The authors of this article have adopted a clinical rule to assist in recognizing promptly those patients in whom the rate of bleeding is sufficiently rapid to make spontaneous recovery unlikely. If the rate of bleeding is such that a stable circulation cannot be

maintained with transfusions roughly approximating 1,500 cc. of blood per 24 hours, emergency operation is in order. However, in upper gastrointestinal hemorrhage, knowledge of the source of bleeding is a prerequisite for emergency surgery. In those patients entering the hospital in shock, both internist and surgeon must follow the case closely, and the patient is preferably treated on the surgical wards.

FRANCIS D. MURPHY.

PLASCHKE, S. J. Vagusresektion als Ulcusoperation [Vagotomy for peptic ulcer]. *Gastroenterologia*, **73**: 240 (1948).

Section of the vagi usually results in an incomplete and temporary suppression of gastric acidity which does not persist for over 2 years. The procedure involves some danger to the gastric mucosa, as it may remove a certain protection. Ulcers have been observed after vagotomy in animal experiments. After vagotomy, a secondary gastroenterostomy often becomes necessary because of disturbed motility. Caution is advised in the use of this operation in the treatment of peptic ulcer. It is only indicated in the so-called "surgically incurable" ulcer.

CHARLES A. FLOOD.

WARREN, R. AND LANMAN, T. H. Surgery in bleeding peptic ulcer. Urgent operation and the principle of exclusion. *Surg. Gyn. Obs.*, **87**: 291 (Sept.) 1948.

This review has a twofold purpose: 1) to examine the need for surgery during the active bleeding stage of peptic ulcer, and 2) to describe a program for handling these patients if the need for operation is established. Under the current methods of treatment, about 5 to 10 per cent of patients, admitted with massive hemorrhage from peptic ulcer, die. Surgery is indicated in these cases with excessive bleeding. Early operation is advocated on all patients over 45 years, in whom hemorrhage persists after 48 hours following admission to the hospital. The surgical procedure of choice is subtotal gastrectomy with removal of the lower two-thirds of the stomach, including the pylorus. In patients in whom the ulcer is difficult to remove, a subtotal gastrectomy with

exclusion, but not removal, of the ulcer is recommended.

FRANCIS D. MURPHY.

COLP, R., KLINGENSTEIN, P., DRUCKERMAN, L. J., AND WEINSTEIN, V. A. A comparative study of subtotal gastrectomy with and without vagotomy. *Ann. Surg.*, **128**: 470 (Sept.) 1948.

The authors compare the early results of subtotal gastrectomy in 54 patients, with those of subtotal gastrectomy and bilateral infradiaphragmatic vagotomy in 46 patients. The latter combined procedure results in achlorhydria after a gruel test meal in a higher percentage of cases than does subtotal gastrectomy alone. While the postoperative morbidity is somewhat greater after gastrectomy with bilateral vagotomy than it is after gastrectomy alone, the mortality rate is no higher in this experience. The slow gastric emptying usually found after vagotomy alone is not present after the combined operation. The follow-up period for the patients has been too short to evaluate the likelihood of development of jejunal ulcer in these two series.

LEMUEL C. MCGEE.

### PROCTOLOGY

GASTON, E. A. The physiology of fecal continence. *Surg. Gyn. Obs.*, **87**: 280 (Sept.) 1948.

The results of a study in normal adults of the mechanism of fecal continence, both colonic and sphincteric, are presented. Five methods, designed for the study of the sphincteric apparatus, are discussed. The findings indicate that, in normal individuals, anal continence is the result of a fine coordination between the rectum and the external anal sphincter. Sphincteric continence will, therefore, be lost with any type of injury which interferes with the function of the external anal sphincter, such as complete division of the external sphincter, transection of the spinal cord, surgical injury of the efferent fibers to the external sphincter, or removal of the afferent fibers of the rectoanal reflex by resection of all of the rectum.

FRANCIS D. MURPHY.

### SURGERY

BEST, R. R. Anastomosis of the ileum to the lower part of the rectum and anus. A report on experiences with ileorectostomy and ileoproctostomy, with special reference to polyposis. *Arch. Surg.*, **57**: 276 (Aug.) 1948.

The chief indications for anastomosing the terminal ileum to the lower part of the rectum or anus are polyposis of the colon and rectum, when carcinoma has developed in the rectum and the patients desire to avoid an ileostomy. Whether or not this procedure will give as many permanent cures as radical abdomino-perineal excision with ileostomy cannot be definitely stated at this time. Improvements in technic are wanting and ileorectostomy or ileoproctostomy should not be attempted in routine cases of rectal carcinoma. Judging from the complications which appeared in these cases, a colostomy should be chosen, in preference to attempting to preserve the sphincter mechanism by sidetracking the colon, until further refinements of technic have been developed. Because of the incidence of rather excessive posterior drainage or development of fistula, establishment of posterior drainage of the presacral space is indicated. Although there was no operative death in this series of 9 cases, the mortality rate would have been rather high if this had not been done. Hypoproteinemia is rather marked in the early postoperative period and efforts must be directed toward a high protein intake.

When the distal ileum is anastomosed to the terminal rectum or anus, it becomes dilated, the wall hypertrophies, and its absorption function and storage capacity apparently increase. Improved technic to afford better security at the line of anastomosis is desirable and would result in fewer of the complications which seem to be the present drawback of the operation. Thus, the operation would have a wider field of usefulness and might serve as a means of preserving the sphincter mechanism in cases of polyposis, in some cases of malignant degeneration of the rectum, and in ulcerative colitis.

ALBERT CORNELL.

SWENSON, O. AND BILL, A. H., JR. Resection of rectum and rectosigmoid with preservation of the sphincter for benign spastic lesions producing megacolon. *Surgery*, **23**: 212 (Aug.) 1948.

Twenty patients, having congenital megacolon with spasm, seen at the Children's Hospital, Boston, have been studied by the authors. A technique, consisting of resection of the rectum and rectosigmoid with preservation of the sphincter, is described. As is pointed out, this method was evaluated in experimental work on 15 dogs, and later the operation successfully used on 3 children.

It is important to remember in applying this technique, that the blood vessels to the proximal end of the bowel are of adequate length to permit the sigmoid to be pulled out through the anus, and that anastomosis be done in two layers with extreme care to prevent leakage into the pelvis.

FRANCIS D. MURPHY.

HOERR, S. O., DUNPHY, J. E., AND GRAY, S. J. The place of surgery in the emergency treatment of acute massive, upper gastrointestinal hemorrhage. *Surg. Gyn. Obs.*, **87**: 338 (Sept.) 1948.

This article discusses the place of surgery in the emergency treatment of acute massive, upper gastrointestinal hemorrhage. The authors feel that the chief indication for operation is not the amount, but the rate, of bleeding as evidenced by syncope or shock despite emergency medical treatment by continuous transfusion.

FRANCIS D. MURPHY.

DIXON, C. F. Anterior resection for malignant lesions of the upper part of the rectum and lower part of the sigmoid. *Ann. Surg.*, **128**: 425 (Sept.) 1948.

In 426 patients, undergoing anterior resection of the sigmoid colon for carcinoma located between 6 and 20 centimeters above the dentate (pectinate) line, there were 25 operative deaths (5.9%). With patients operated upon for lesions in this location in the past 7 years, the surgical mortality rate has been only 2.6 per cent. The operation was performed sufficiently long ago to study survival rates in 272 patients. Sixty-seven per cent were alive after 5

years; 50 per cent were alive after 10 years. The best results were obtained in the removal of lesions occurring 11 to 15 centimeters above the dentate line.

LEMUEL C. MCGEE.

## PHYSIOLOGY: SECRETION

GROSSMAN, M. I. AND ROBERTSON, C. R. Inhibition by histaminase of gastric secretion in dogs. *Am. J. Physiol.*, **153**: 447 (June) 1948.

Twenty units per kg. of histaminase from hog renal cortex given intravenously markedly inhibits the gastric secretory response to 0.0125 mg. histamine dihydrochloride in dogs. The secretory response to food and parasympathomimetic drugs is also inhibited. The effect may be due to the histaminase or some other constituent of the extract.

ARTHUR E. MEYER.

POTH, E. J., MANHOFF, L. J., AND DELOACH, A. W. The relation of pancreatic secretion to peptic ulcer formation. *Surgery*, **23**: 62 (July) 1948.

This study is primarily concerned with the influence of secretory activity of the pancreas upon ulcer formation in the dog. Histamine-in-beeswax was injected into 4 groups of dogs in order to observe the tendency for peptic ulcer formation: (1) a control group, (2) those subjected to total pancreatectomy, (3) those having ligation of the pancreatic ducts, and (4) those rendered diabetic with alloxan. It is concluded that neutralizing alkaline secretions are important in the prevention of ulcer formation and that whenever the pancreatic ducts—duodenum relationship is destroyed, secretions should be returned to the proximal portions of the bowel to neutralize the acid effluent of the stomach.

FRANCIS D. MURPHY.

WANG, C. C., GROSSMAN, M. I., AND IVY, A. C. Effect of secretin and pancreozymin on amylase and alkaline phosphatase secretion by the pancreas in dogs. *Am. J. Physiol.*, **154**: 358 (Aug.) 1948.

Continuous administration of secretin to the dog causes an increase in the volume of



pancreatic juice but does not increase the enzyme production per minute. Pancreozymin stimulates the amylase output of the pancreas but not that of alkaline phosphatase. The source of enzyme production is probably not the same for phosphatase as for the other three major enzymes. The proposal suggested by Jacoby, that the ductule cells are responsible for the production of the phosphatase and the acinar cells for the other three enzymes, is thus supported.

ARTHUR E. MEYER.

### METABOLISM AND NUTRITION

WILLIAMS, R. H., DAUGHADAY, W. H., ROGERS, W. F., JR., ASPER, S. P., JR., AND TOWERY, B. T. Obesity and its treatment, with particular reference to the use of anorexigenic compounds. *Ann. Int. Med.*, 29: 510 (Sept.) 1948.

The etiologic aspects of obesity are discussed. Emphasis is placed on emotional factors, family influence, and eating habits. Clinical studies have ascertained endocrine imbalance not to be a significant factor. Some obese patients have even gained weight under thyroid medication, presumably as a result of increased appetite. The regimen outlined consisted of acquainting the patient with the caloric value of various foods, and with the emotional and environmental factors involved. Whenever the goal was not obtained by such methods, anorexic compounds of aminopropane type (dextrine and others) were used with good results as adjunctive therapy. The undesirable effects of the drug were greatly minimized by

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L. T. ROSENTHAL.

### MISCELLANEOUS

OSTRUM, H. W. AND SERBER, W. Tuberculosis of the stomach and duodenum. *Am. J. Roent. Rad. Therapy*, 60: 315 (Sept.) 1948.

Two cases of tuberculosis of the stomach and one of the duodenum are described. In all 3 cases, the lungs showed no active pulmonary tuberculosis. One patient had a peripheral tuberculous adenitis for years, and in each case abdominal lymph node involvement was a prominent feature. All of the patients developed perforations or fistulous tracts at the site of their lesions. From the roentgenological standpoint, there were no pathognomonic findings. Ulcerative and infiltrative lesions can easily be confused with benign ulcer or carcinoma. A combination of both types of lesions, as well as extensive mucosal nodularity, might be suggestive. The most significant findings than can be demonstrated roentgenologically are simultaneous involvement of the stomach and duodenum, the presence of fistulae or sinuses, and signs of external pressure by enlarged lymph nodes.

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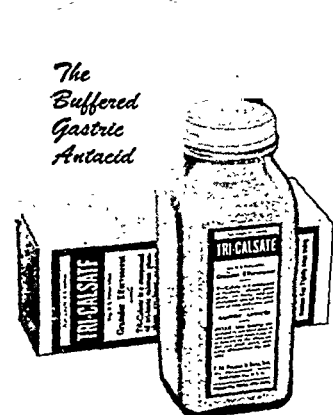
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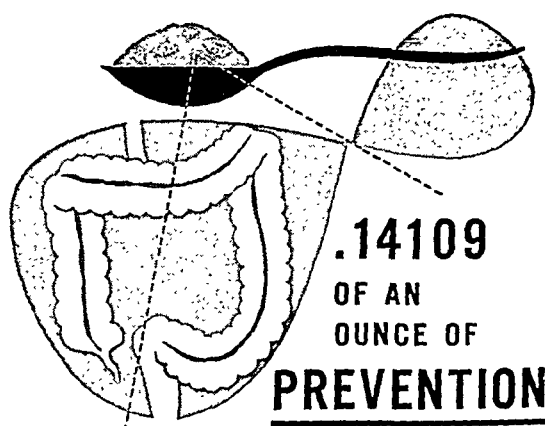
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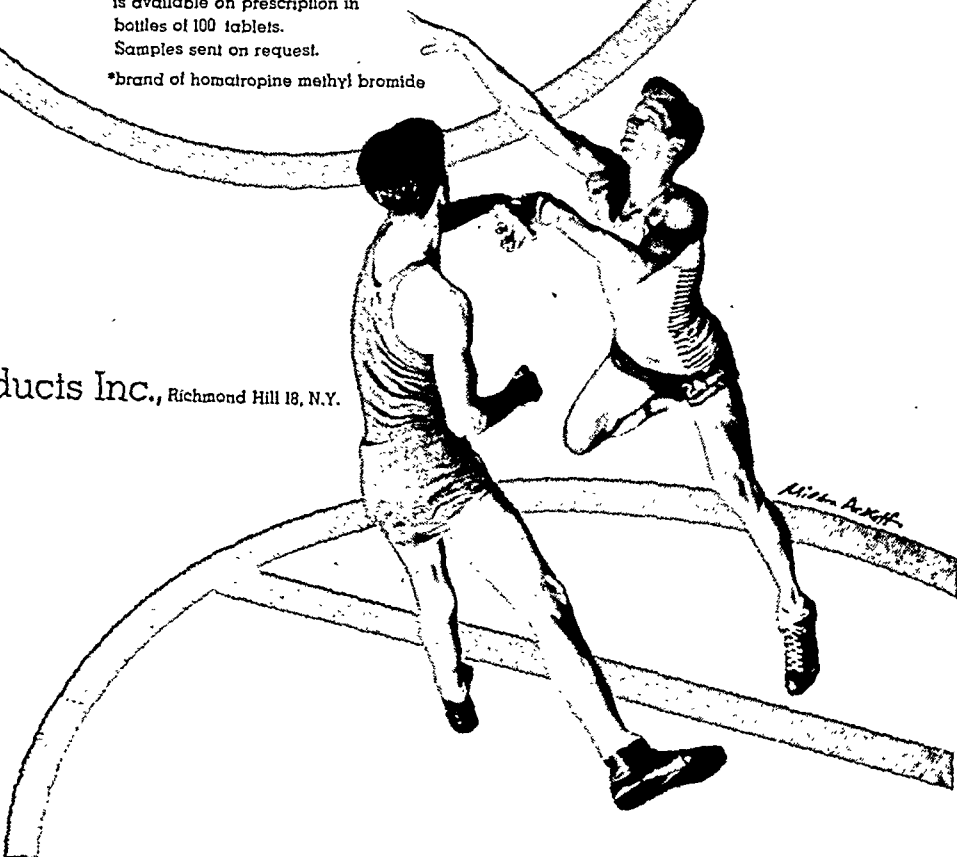
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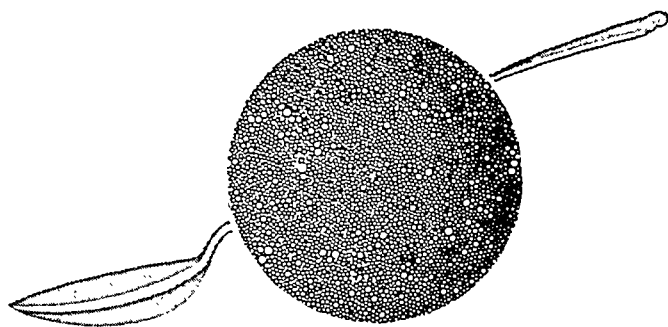
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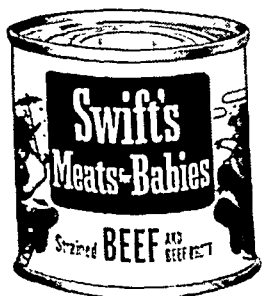
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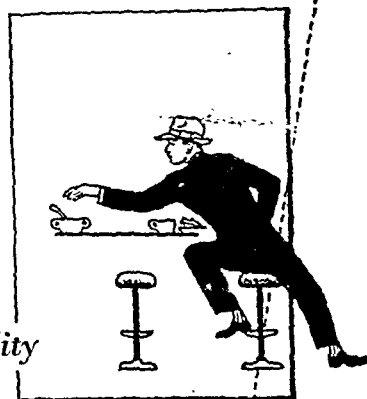
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